(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 July 2004 (22.07.2004)

PCT

(10) International Publication Number
WO 2004/060367 A1

(51) International Patent Classification[7]: A61K 31/4164, 31/4196, C07D 233/54, 233/90, 249/08, 403/12, 401/04, A61P 29/00

(21) International Application Number:
PCT/JP2003/015921

(22) International Filing Date:
12 December 2003 (12.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

2002953602	30 December 2002 (30.12.2002)	AU
2003901804	15 April 2003 (15.04.2003)	AU
2003903928	28 July 2003 (28.07.2003)	AU

(71) Applicant *(for all designated States except US)*: **FUJISAWA PHARMACEUTICAL CO., LTD.** [JP/JP]; 4-7, Doshomachi 3-chome,, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TAKAHASHI, Fumie** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku,, Osaka-shi, Osaka 541-8514 (JP). **NAKAGAWA, Toshiya** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). **MATSUSHIMA, Yuji** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). **NAKAMURA, Katsuya** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).

(74) Agent: **TABUSHI, Eiji**; c/o Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaki-shi, Osaka 532-8514 (JP).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

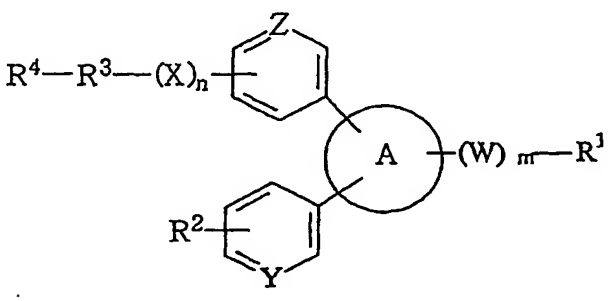
(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/060367 A1

(54) Title: IMIDAZOLE AND TRIAZOLE DERIVATIVES USEFUL AS SELECTIVE COX-1 INHIBITORS



(I)

(57) Abstract: A compound of the formula (I): or salts thereof, which are useful for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, thrombosis, cancer or neurodengenerative diseases.

D E S C R I P T I O N

AZOLE COMPOUNDS

Technical Field

This invention relates to new azole compounds having pharmacological activity, to a process for their production and to a pharmaceutical composition containing the same.

Background Art

The presence of two cyclooxygenase isoenzymes, cyclooxygenase-I (COX-I) and cyclooxygenase-II (COX-II) is known (Proc. Nat. Acad. Sci. USA 88, 2692-2696 (1991)).

Traditional non steroidal anti-inflammatory compounds (NSAIDs) have inhibiting activities of both COX-I and COX-II (J. Biol. Chem., 268, 6610-6614 (1993), etc). The therapeutic use thereof involves undesired effects on the gastrointestinal tract, such as bleeding, erosions, gastric and intestinal ulcers, etc.

It was reported that selective inhibition of COX-II shows anti-inflammatory and analgesic activities comparable with conventional NSAIDs but with a lower incidence of some gastrointestinal undesired effects (Pro. Nat. Acad. Sci. USA, 91, 3228-3232(1994)). Accordingly, various selective COX-II inhibitors have been prepared. However, it was reported that those "selective COX-II inhibitor" show some side-effects on kidney and/or insufficient efficacy on acute pains.

Further, some compounds such as SC-560, mofezolac, etc, which have certain selective inhibiting activity against COX-I. WO98/57910 shows some compounds having such activity. However, their selectivity of inhibiting COX -I does not seem to be enough to use them as a clinically acceptable and satisfactory analgesic agent due to their gastrointestinal disorders.

WO02/055502 shows some pyridine derivatives having cyclooxygenase inhibiting activity, particularly cyclooxygenase-I inhibiting activity. Further, WO03/040110

shows some triazole derivatives having cyclooxygenase inhibiting activity, particulary cyclooxygenase-I inhibiting activity. And WO99/51580 shows some triazole derivatives having an inhibiting activity of cytokine production.

Disclosure of Invention

This invention relates to azole compounds, which have pharmacological activity such as cyclooxygenase (hereinafter described as COX) inhibiting activity, to a process for their production, to a pharmaceutical composition containing the same and to a use thereof.

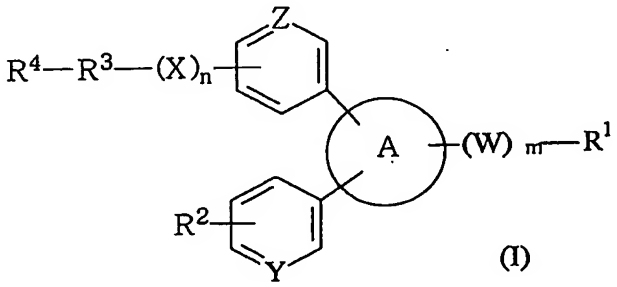
Accordingly, one object of this invention is to provide the azole compounds, which have a COX inhibiting activity.

Another object of this invention is to provide a process for production of the azole compounds.

A further object of this invention is to provide a pharmaceutical composition containing, as active ingredients, the azole compounds.

Still further object of this invention is to provide a use of the azole compounds for manufacturing a medicament for treating or preventing various diseases.

The new azole compounds of this invention can be represented by the following general formula (I):



(I)

wherein R^1 is lower alkyl optionally substituted with suitable substituent(s); cyclo(lower)alkyl; lower alkynyl; cyano; acyl; heterocyclic group; lower

alkenyl; lower alkoxy optionally substituted with lower alkoxy, N,N-di(lower)alkylcarbamoyl, cyclo(lower)alkyl, aroyl or halogen; or cyclo(lower)alkyloxy;

R^2 is lower alkyl, lower alkoxy, cyano or 1H-pyrrol-1-yl;

R^3 is lower alkylene or lower alkenylene;

R^4 is hydroxy, protected hydroxy, amino, protected amino, acylamino, acyl, cyano or heterocyclic group;

X is O, S, SO or SO_2;

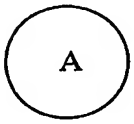
Y is CH or N;

Z is CH or N;

W is O, S, SO or SO_2;

m is 0 or 1;

n is 0 or 1; and

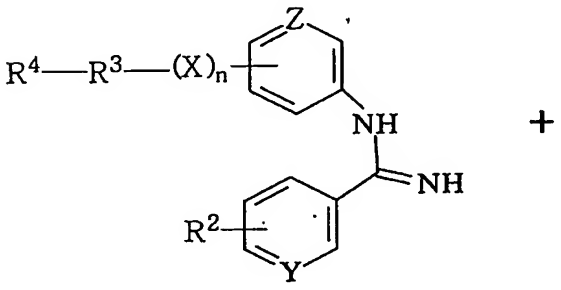


is triazole or imidazole;

or salts thereof.

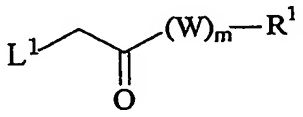
The object compound (I) of the present invention can be prepared by the following processes.

Process (1)

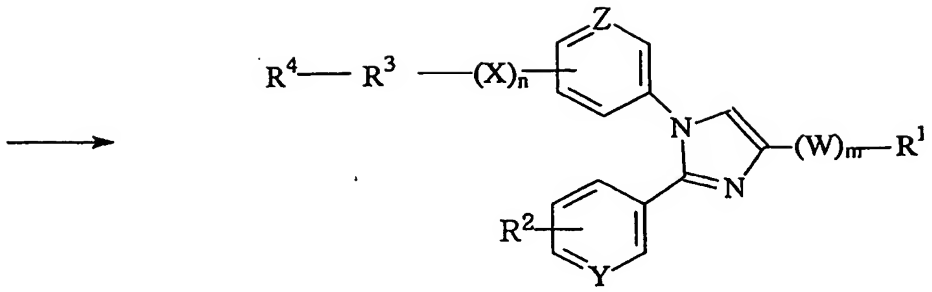


(II) or its salt

+

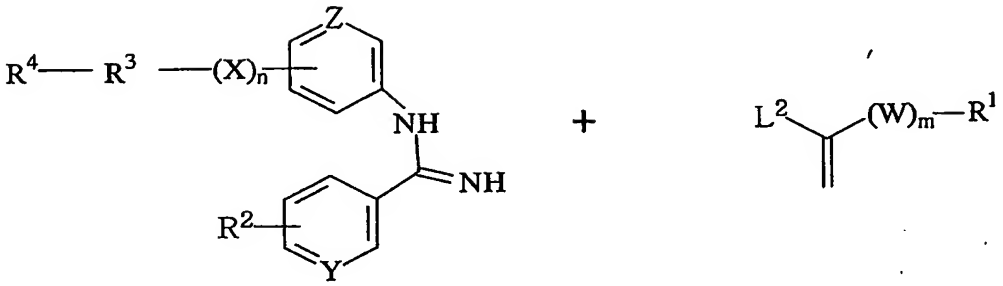


(III) or its salt



(Ia) or its salt

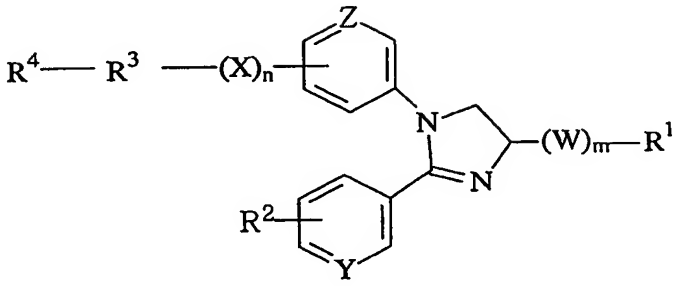
Process (2)



(II) or its salt

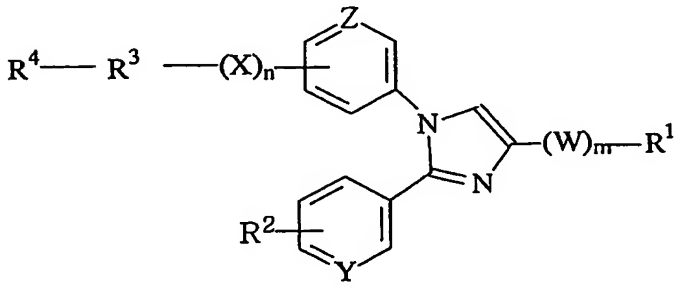
(IV) or its salt

(2)-1



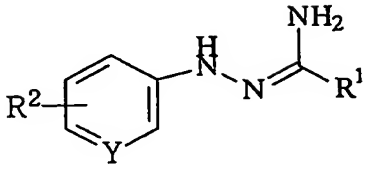
(V) or its salt

(2)-2

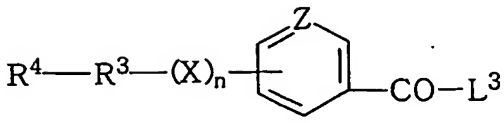


(Ib) or its salt

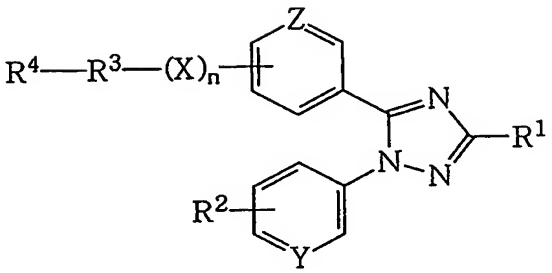
Process (3)



(VI) or its salt

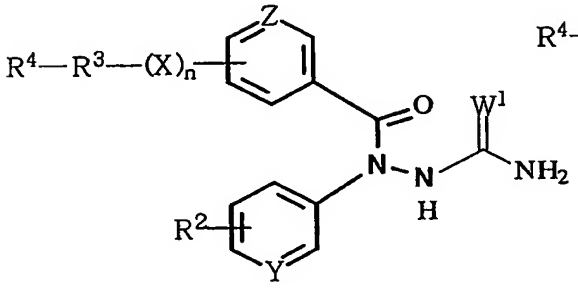


(VII) or its salt

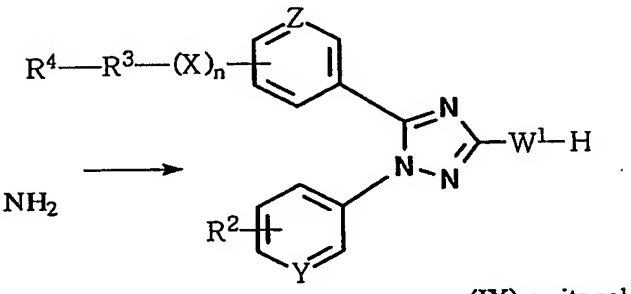


(Ic) or its salt

Process (4)

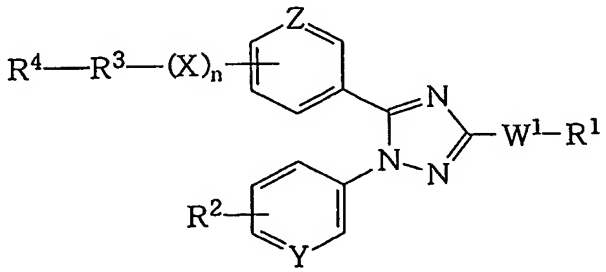


(VIII) or its salt



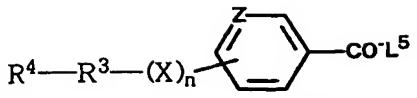
(IX) or its sal

R^1-L^4

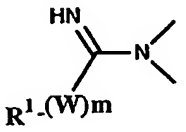


(Id) or its salt

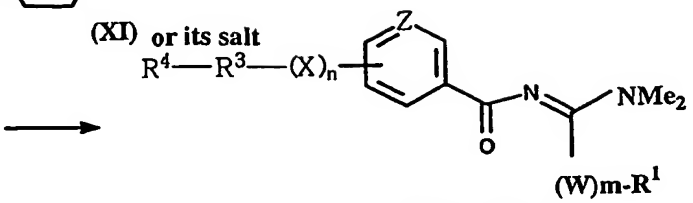
Process (5)



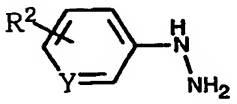
(XI) or its salt



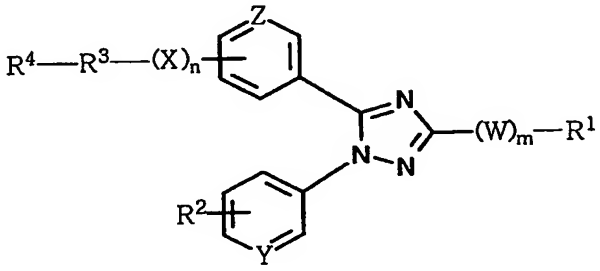
(X) or its salt



(XII) or its salt

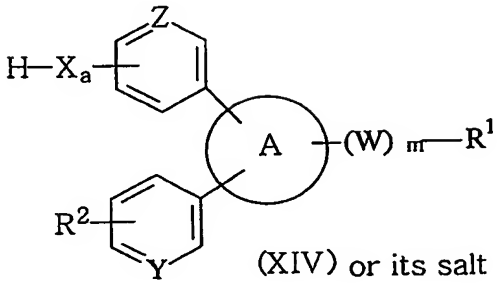


(XIII) or its salt



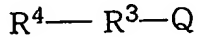
(Ie) or its salt

Process (6)

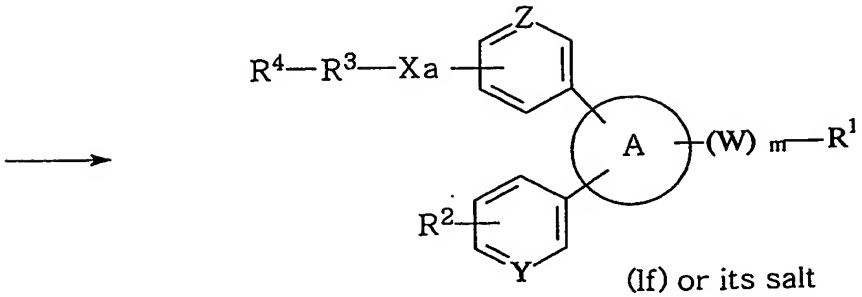


(XIV) or its salt

+



(XV) or its salt



(If) or its salt

In the above processes, R^1, R^2, R^3, R^4, W, X, Y, m, n and

(A) are each as defined above,

L^1 is a leaving group,

L^2 is a leaving group,

L^3 is a leaving group,

W^1 is O or S,

L^4 is a leaving group,

L^5 is a leaving group,

Xa is O or S, and

Q is hydroxy or a leaving group.

The compounds of formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. This invention includes both mixtures and separate individual isomers.

The compounds of the formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

The compounds of the formula (I) and its salts can be in a form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

Also included in the scope of invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

The lower moiety in the terms "lower alkenyl", "lower

alkynyl" and "lower alkenylene" is intended to mean a group having 2 to 6 carbon.

Suitable "lower alkyl", and lower alkyl moiety in the terms "lower alkylsulofonyl" and halo(lower)alkyl may be a straight or branched C_1-C_6 alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, ethylpropyl, hexyl or the like, in which preferable one is methyl, propyl or isopropyl.

Suitable "lower alkoxy" and lower alkoxy moiety in the term "lower alkoxyimino" may be a straight or branched C_1-C_6 alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, hexoxy, or the like, in which preferable one is methoxy, ethoxy or isopropoxy.

Suitable "halogen" may be fluoro, chloro, bromo or iodo or the like.

Suitable "cyclo(lower)alkyl", and cyclo(lower)alkyl moiety in the terms "cyclo(lower)alkylcarbonyl" and "cyclo(lower)alkyloxy" may include 3 to 8-membered cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like, preferably one having 3 to 6 carbon atoms, and more preferable one is cyclopropyl, cyclopentyl or cyclohexyl.

Suitable alkynyl may be a monovalent branched or unbranched hydrocarbon radical containing at least one carbon-carbon triple bond, for example ethynyl, 2-propynyl, 2-butynyl, and the like.

Suitable "lower alkylene" may be a straight or branched C_1-C_6 alkylene such as methylene, ethylene, trimethylene, propylene, tetramethylene, pentamethylene, hexamethlyene, ethylethylene, or the like, in which preferable one is methylene, ethylene or trimethylene.

Suitable "lower alkenyl" may be a straight or branched C_2-C_6 alkeny such as ethenyl, propenyl, butenyl, pentenyl, hexenyl, isopropenyl, butadienyl, pentadienyl, hexadienyl or the like, in which preferable one is isopropenyl.

Suitable "lower alkenylene" may be a straight or branched chain aliphatic hydrocarbon divalent group having more than one double bond between two carbon atoms, such as ethenylene,

propenylene, methylethenylene, butenylene, methylpropenylene, dimethylpropenylene, pentenylene, hexenylene or the like, and it is preferably (C_2-C_4)alkenylene.

Suitable "heterocyclic group" may be one containing at least one hetero atom selected from nitrogen, sulfur and oxygen atom, and may include saturated or unsaturated, monocyclic or polycyclic heterocyclic group, and preferable heterocyclic group may be N-containing heterocyclic group such as unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl [e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.], tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.;

saturated 3 to 7-membered heteromonocyclic group containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, homopiperazinyl; etc.];
unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, imidazopyridyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g. tetrazolo[1,5-b]pyridazinyl, etc.], quioxalinyl, etc.;
unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.;
saturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, 1H-tetrahydropyranyl, tetrahydrofuranyl, etc.;
unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms, for example, thienyl, etc.;
unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.], oxazolinyl [e.g. 2-oxazolinyl, etc.], etc.;
saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl,

etc.];
unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzofurazanyl, benzoxazolyl, benzoxadiazolyl, etc.];
unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g. 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.], etc.;
saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g. thiazolidinyl, etc.];
unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g. benzothiazolyl, benzothiadiazolyl, etc.];
unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms [e.g. benzofuranyl, benzodioxolyl, chromanyl, etc.] and the like.

Said "heterocyclic group" may be substituted with lower alkyl as exemplified above or oxo, in which preferable one is pieridyl or oxoimidazolidinyl.

Suitable "acyl" and acyl moiety in the term "acylamino" may be carboxy; esterified carboxy; carbamoyl; carbamoyl substituted with lower alkyl, aryl, ar(lower)alkyl, arylsulfonyl, lower alkylsulfonyl, a heterocyclic group; or halo(lower)alkyl. substituted or unsubstituted arylsulfonyl; substituted or unsubstituted lower alkylsulfonyl; cyclo(lower)alkylcarbonyl; lower alkanoyl; substituted or unsubstituted aroyl;
a heterocycliccarbonyl and the like.

The esterified carboxy may be substituted or unsubstituted lower alkoxycarbonyl [e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, hexyloxycarbonyl, 2-iodoethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, etc.], substituted or unsubstituted aryloxycarbonyl [e.g. phenoxycarbonyl, 4-nitrophenoxycarbonyl, 2-naphthyloxycarbonyl, etc.], substituted or unsubstituted ar(lower)alkoxycarbonyl [e.g.

benzyloxycarbonyl, phenethyloxycarbonyl, benzhydryloxycarbonyl, 4-nitrobenzyloxycarbonyl, etc.] and the like, in which preferable one is unsubstituted lower alkoxycarbonyl and more preferable one is ethoxycarbonyl.

The carbamoyl substituted with lower alkyl may be a carbamoyl group substituted with the same or different above lower alkyl groups on nitrogen atom, such as methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, diisopropylcarbamoyl, N-methyl-N-ethylcarbamoyl or the like. It is preferably di(C_1-C_4)carbamoyl, more preferably di(C_1-C_2 alkyl)carbamoyl.

The carbamoyl substituted with aryl may be phenylcarbamoyl, naphthylcarbamoyl, lower alkyl-substituted phenylcarbamoyl [e.g. tolylcarbamoyl, xylylcarbamoyl, etc.] and the like.

The carbamoyl substituted with ar(lower)alkyl may be benzylcarbamoyl, phenethylcarbamoyl, phenylpropylcarbamoyl and the like, in which preferable one is benzylcarbamoyl.

The carbamoyl substituted with arylsulfonyl may be phenylsulfonylcarbamoyl, tolylsulfonylcarbamoyl and the like.

The carbamoyl substituted with lower alkylsulfonyl may be methylsulfonylcarbamoyl, ethylsulfonylcarbamoyl and the like.

The carbamoyl substituted with a heterocyclic group may be one substituted with a heterocyclic group as mentioned above.

The carbamoyl substituted with halo(lower)alkyl may be chloromethylcarbamoyl, brommethylcarbamoy, chloroethylcarbamoyl, bromomethylcarbamoyl, chloropropylcarbamoyl, bromopropylcarbamoyl and the like, in which preferable one is chloropyopylcarmamoyl.

The lower alkanoyl may be formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl and the like, in which preferable one is acetyl, propionyl or isobutyryl.

The substituted or unsubstituted aroyl may be benzoyl, naphthoyl, toluoyl, di(tert-butyl)benzoyl, halo(lower)alkoxybenzoyl [e.g. trifluoromethoxybenzoyl, etc.] and the like, in which preferable one is benzoyl or trifluoromethoxybenzoyl.

The substituted or unsubstituted arylsulfonyl may be phenylsulfonyl, tolylsulfonyl, halophenylsulfonyl [e.g. fluorophenylsulfonyl, etc.] and the like, in which preferable one is fluorophenylsulfonyl.

The substituted or unsubstituted lower alkylsulfonyl may be methylsulfonyl, ethylsulfonyl, halo(lower)alkylsulfonyl (e.g. trifluoromethylsulfonyl, etc.) and the like, in which preferable one is methylsulfonyl or trifluorometylsulfonyl.

The cyclo(lower)alkylcarbonyl may be 3 to 8-membered cycloalkylcarbonyl such as cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl or cyclohexylcarbonyl, in which preferable one is cyclopropylcarbonyl or cyclohexylcarbonyl.

The heterocyclic moiety in the term "a heterocycliccarbonyl" may be one mentioned above as a heterocyclic group, in which preferable one is piperidyl.

Suitable example of "hydroxy protective group" in the term of "protective hydroxy" may include acyl [e.g. lower alkanoyl, lower alkylsulfonyl, halo(lower)alkylsulfonyl (e.g. trifluoromethysulfonyl, etc.), etc.] as mentioned above, phenyl(lower)alkyl which may be one or more suitable substituent(s) (e.g. benzyl, 4-methoxybenzyl, trityl, etc.), tri-substituted silyl [e.g. tri(lower)alkylsilyl (e.g. trimetylsilyl, tert-butyldimetylsilyl, etc.), tert-butyldiphenylsilyl, etc.], tetrahydropyranyl and the like, in which preferable one is lower alkanoyl, lower alkylsulfonyl or phenyl(lower)alkyl.

Suitable "a leaving group" may be halogen (e.g. fluoro, chloro, bromo, iodo), arenesulfonyloxy (e.g. benzenesulofonyloxy, tosyloxy, etc.), alkanesulofnyloxy (e.g. mesyloxy, ethanesulfonyloxy, etc.), and the like, in which preferable one is halogen.

Suitable example of "N-protective group" in the term of "protected amino" may be common N-protective group such as substituted or unsubstituted lower alkanoyl [e.g. formyl, acetyl, propionyl, trifluoroacetyl, etc.], phthaloyl, lower

alkoxycarbonyl [e.g. tert-butoxycarbonyl, tert-amyloxycarbonyl, etc.], substituted or unsubstituted aralkyloxycarbonyl [e.g. benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, etc.], 9-fluorenylmethoxycarbonyl, substituted or unsubstituted arenesulfonyl [e.g. benzenesulfonyl, tosyl, etc.], nitrophenylsulfenyl, aralkyl [e.g. trityl, benzyl, etc.] or the like, in which preferable one is phthaloyl or lower alkoxycarbonyl.

Preferred "suitable substituent" as the substituent of lower alkyl for R^1 may be halo(lower)alkoxy, lower alkenyl, lower alkynyl, lower alkylamino, acylamino, acyl, lower alkylsily, lower alkoxy, aryl, acyloxy, hydroxy, nitro, amino, cyano, halogen, aryloxy, lower alkylthio, lower alkoxyimino and the like.

Preferred "lower alkyl substituted with suitable substituten(s)" for R^1 may be lower alkyl substituted with one or more halogen atom(s) or lower alkoxyimino.

More preferred "lower alkyl substituted with one or more halogen atom(s)" may be lower alkyl substituted with 1 to 5 (more preferably 1 to 3) above halogen atom(s), such as fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl, tribromomethyl, fluoroethyl, chloroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 2,2,3,3,3-pentafluoroethyl, fluoropropyl, fluorobutyl, fluorohexyl, or the like, in which preferable one is halogen-substituted C_1-C_2 alkyl. More preferable one is fluorine-substituted methyl, and most preferable one is difluoromethyl or trifluoromethyl.

More preferred "lower alkyl substituted with lower alkoxyimino" may be methoxyiminoethyl (e.g. 1-methoxyiminoethyl, 2-methoxyiminoethyl), methoxyiminomethylpropyl (e.g. 1-methoxyimino-2-methylpropyl, etc.) and the like, in which preferable one is 1-methoxyiminoethyl or 1-methoxy-2-methylpropyl.

Preferred "acyl" for R^1 may be lower alkanoyl, carbamoyl substituted with lower alkyl, cylo(lower)alkylcarbonyl, aroyl,

or heterocycliccarbonyl mentioned above.

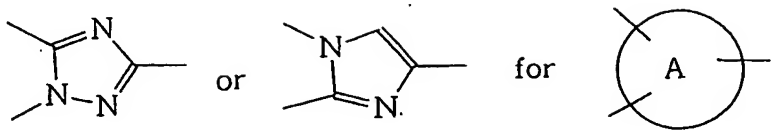
Preferred "lower alkoxy substituted with lower alkoxy" for R^1 may be methoxymethoxy, methoxyethoxy, ethoxymethoxy, ethoxyethoxy and the like, in which preferable one is ethoxyethoxy.

Preferred "lower alkoxy substituted with halogen" for R^1 may be lower alkoxy substituted with one or more (more preferably 1 to 5, most preferably 1 to 3) above halogen atom(s), such as fluoromethoxy, chloromethoxy, difluomomethoxy, dichloromethoxy, dibromomethoxy, trifluoromethoxy, trichloromethoxy, fluoroethoxy, chloroethoxy, 2,2-difluoroethoxy, 2,2-dichloroethoxy, 2,2,2-trifluoroethoxy, 2,2,2-trichloroethoxy, 2,2,3,3-pentafluoroethoxy, fluoropropoxy, fluorobutoxy, fluorohexyloxy, or the like, and it is preferably (C_1-C_4)alkoxy substituted with halogen, more preferably (C_1-C_2)alkoxy substituted with halogen, more preferably (C_1-C_2)alkoxy substituted with fluorine, more preferably ethoxy substituted with fluorine, most preferably 2,2-difluroethoxy or 2,2,2-trifluoroethoxy.

Preferred "acylamino" for R^4 may be carbamoylamino, lower alkylsufonylamino, lower alkanoylamino or sulfamoylamino.

Preferred "acyl" for R^4 may be carboxy, esterified carboxy, carbamoyl or lower alkylsulfonyl mentioned above.

Preferred compound (I) is one having lower alkyl optionally substituted with one or more halogen atom(s); cyclo(lower)alkyl; lower alkanoyl; carbamoyl substituted with lower alkyl; cyclo(lower)alkylcarbonyl; aroyl; or heterocycliccarbonyl for R1; lower alkoxy for R2; lower alkylene or lower alkenylene (more preferably lower alkylene) for R3; hydroxy, protected hydroxy, amino, protected amino, acylamino, acyl or cyano (more preferably hydroxy, amino, carbamoylamino, lower alkylsulfonylamino, lower alkanoylamino, sulfamoylamino or lower alkylslufonyl) for R4; O for X; CH or N for Y; CH for Z; O for W; 0 or 1 for m; 0 or 1 for n; and



Suitable salts of the compounds (I) are pharmaceutically acceptable conventional non-toxic salts and include a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, etc.), an organic acid salt (e.g. acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), or the like.

The processes for preparing the object compounds are explained in detail in the following.

Process (1)

The object compound (Ia) or its salt can be prepared by reacting a compound (II) or its salt with a compound (III) or its salt in the presence of base to form imidazole ring.

Suitable salts of the compounds (II) or (III) may be the same as those exemplified for the compound (I).

The base employable in this process for making basic condition is not particularly limited so long as it accelerate this reaction and may include alkali metal bicarbonate (e.g. lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, etc.), alkali metal carbonate (e.g. lithium carbonate, sodium carbonate, potassium carbonate, etc.), alkaline earth metal carbonate (e.g. magnesium carbonate, calcium carbonate, etc.), alkali metal hydroxide (e.g. lithium hydroxide, sodium hydroxide, potassium hydroxide, etc.), etc., in which preferable one is

alkali metal bicarbonate, especially sodium bicarbonate.

The reaction is carried out in a conventional solvent such as an alcohol (e.g. methanol, ethanol, propanol, isopropanol, etc.), diisopropyl ether, tetrahydrfuran, dioxane, etc, or a mixture of thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

According to the starting material, the heterocyclic ring is formed but not to form imidazole ring. In such case, the dehydration process is need to form imidazole ring.

The dehydration process is carried out in the hot and acidic condition.

The solvent employable in this process is not particularly limited, but acid such as acetic acid, sulfuric acid or the like may be used as solvent.

Process (2)

The object compound (Ib)or its salt can be prepared by reacting a compound (II) or its salt with a compound (IV) or its salt.

In this process, first, a compound (II) or its salt is condensed to a compound (IV) or its salt for synthesis a compound (V) or its salt (Process (2)-1).

Suitable salts of the compounds (II), (IV) or (V) may be the same as those exemplified for the compound (I).

Process (2)-1 is carried out under in the presence of Hunig's base (N,N-diisopropylethylamine).

The reaction is carried out in a conventional solvent such as diisopropyl ether, tetrahydrfuran, dioxane.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process (2)-2 is the oxidation process to form imidazole ring in the presence of catalyst.

The oxidative catalyst employable in this process is not particularly limited so long as it can catalyze the reaction from 4,5-dihydro-imidazole derivative to imidazole derivative

and include manganese (IV) oxide (MnO_2).

The solvent in this process is not particularly limited so long as it is inactive in this reaction and may include amides such as N,N-dimethylformamide, dimethylacetamide, hexamethylphosophoric triamide; aromatic hydrocarbon such as benzene, toluene; or the like.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process (3)

The object compound (Ic) or its salt can be prepared by reacting a compound (VI) or its salt with a compound (VII) or its salt.

The reaction is usually carried out in a conventional solvent such tetrahydrofuran, dioxane, chloroform, methylene chloride, dimethyl acetamide, N,N-dimethylformamide or any other organic solvent which does not adversely influence the reaction.

This reaction is preferably carried out in the presence of an inorganic or an organic base such as an alkali metal hydroxide, an alkali metal hydrogencarbonate, alkali metal carbonate, alkali metal acetate, tri(lower)alkylamine, pyridine (e.g. pyridine, lutidine, picoline, dimethylaminopyridine, etc.), N-(lower)alkylmorpholine, N-,N-di(lower)alkylbenzylamine, N-,N-di(lower)alkylaniline or the like. When the base, the acid and/or the starting compound are in liquid, they can be used also as a solvent.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process (4)

The compound (IX) or its salt can be prepared by converting a compound (VIII) or its salt under basic condition.

The reaction is usually carried out in a conventional solvent such as water, alcohols (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, chloroform, methylene chloride, dimethyl acetamide, N,N-dimethylformamide

or any other organic solvent which does not adversely influence the reaction. Among these solvents, hydrophilic solvents may be used in a mixture with water.

This reaction is preferably carried out in the presence of an inorganic or an organic base such as an alkali metal hydroxide, an alkali metal hydrogencarbonate, alkali metal carbonate, alkali metal acetate, tri(lower)alkylamine, pyridine (e.g. pyridine, lutidine, picoline, dimethylaminopyridine, etc.), N-(lower)alkylmorpholine, N-,N-di(lower)alkylbenzylamine, N-,N-di(lower)alkylaniline or the like. When the base, the acid and/or the starting compound are in liquid, they can be used also as a solvent.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Subsequently, the obtained compound (IX) is condensed with R^1-L^4 under basic condition to give a compound (Id).

The reaction is usually carried out in a conventional solvent as exemplified in Process 3, or any other organic solvent which does not adversely influence the reaction. Among these solvents, hydrophilic solvents may be used in a mixture with water.

The suitable base may include a tertiary amine [e.g. triethylamine, pyridine, N,N-dimethylaniline, etc.], an alkali metal hydroxide [e.g. sodium hydroxide, potassium hydroxide, etc.], an alkali metal carbonate [e.g. sodium carbonate, potassium carbonate, etc.], alkali metal bicarbonate (e.g. sodium bicarbonate, etc.), a salt of an organic acid [e.g. sodium acetate, etc.] and the like. In case that the base is liquid, the base can be used as a solvent.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process (5)

The compound (XII) or its salt can be prepared by reacting a compound (X) or its salt with a compound (XI) or its salt under basic condition.

The reaction is usually carried out in a suitable solvent such as acetates, tetrahydrofuran, dioxane, chloroform, methylene chloride, dimethyl acetamide, N,N-dimethylformamide or any other organic solvent which does not affect the reaction.

This reaction is preferably carried out in the presence of an inorganic or an organic base such as an alkali metal hydrogencarbonate, alkali metal carbonate, alkali metal acetate, trialkylamine, pyridine (e.g. pyridine, lutidine, picoline, dimethylaminopyridine, etc.), N-alkylmorpholine, N-,N-dialkylbenzylamine, N-,N-dialkylaniline and so on. In case base, acid and/or starting compound are liquid, they can play a role of solvent.

The reaction temperature is not critical to the reaction in the yield or purity and the reaction is allowed to be carried out independent of temperature.

Subsequently, the compound (XII) or its salt is reacted with a compound (XIII) or its salt under acidic condition to give a compound (Ie) or its salt. When a salt of the compound (XIII) is used in this reaction, a suitable base may be added to neutralize the system.

The reaction is usually carried out in a suitable solvent such as water, acetic acid, methanol, tetrahydrofuran, dioxane, chloroform, methylene chloride, dimethyl acetamide, N,N-dimethylformamide or any other organic solvent which does not affect the reaction. In addition, a mixed solvent is allowed to be used.

The suitable acid may include an organic carboxylic acid [e.g. formic acid, acetic acid, propionic acid, etc.), an organic sulfonic acid [e.g. methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.], a mineral acid [e.g. hydrochloric acid, sulfuric acid, etc.]. In case where the acid is liquid, it can play a role of solvent.

The reaction temperature is not critical to the reaction in the yield or purity and the reaction is allowed to be carried out independent of temperature.

Process (6)

The object compound (If) or its salt can be prepared by reacting a compound (XIV) or its salt with a compound (XV) or its salt.

Suitable salts of the compounds (If), (XIV) and (XV) may be the same as those exemplified for the compound (I).

When the compound (XV) having halogen for Q is used in this reaction, the reaction is preferably carried out in the presence of a base such as alkali metal (e.g. sodium, potassium, etc.), an alkaline earth metal (e.g. magnesium, calcium, etc.), the hydride or hydroxide or carbonate or bicarbonate thereof.

When the compound (XV) having hydroxy for Q is used in this reaction, the reaction is preferably carried out in the presence of diethyl azodicarboxylate and triphenylphosphine.

The reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, dioxane, a alcohol (e.g. methanol, ethanol, etc.), acetonitrile, tetrahydrofuran, acetic acid, N,N-dimethylformamide, or a mixture thereof.

The reaction temperature is not critical and the reaction can be carried out under cooling to heating.

In order to illustrate the usefulness of the object compounds (I), the pharmacological test data of the compounds (I) are shown in the following.

[A] ANALGESIC ACTIVITY:

Effect on adjuvant arthritis in rats:

(i) Test Method:

Arthritis was induced by injection of 0.5 mg of Mycobacterium tuberculosis (Difco Laboratories, Detroit, Mich.) in 50 μl of liquid paraffin into the right hind footpad of Lewis rats aged 7 weeks. Analgesic activity of a single dose of agents in arthritic rats was studied. Arthritic rats were randomized and grouped (n=10) for drug treatment based on pain threshold of left hind

paws and body weight on day 22. Drugs (Test compounds) were administered and the pain threshold was measured 2hr after drug administration. The intensity of hyperalgesia was assessed by the method of Randall - Selitto. The mechanical pain threshold of the left hind paw (uninjected hind paw) was determined by compressing the ankle joint with a balance pressure apparatus (Ugo Basile Co.Ltd., Varese, Italy). The threshold pressure of rats squeaking or struggling was expressed in grams. The threshold pressure of rats treated with drugs was compared with that of non-treated rats. A dose showing the ratio of 1.5 is considered to be the effective dose.

(ii) Test Results:

Test compound (Example No.)	Dose (mg/kg)	The coefficient of analgesic
33	3.2	>= 1.5
34	3.2	>= 1.5
36	3.2	>= 1.5
37	3.2	>= 1.5
43	3.2	>= 1.5
48	3.2	>= 1.5
63	3.2	>= 1.5
77	3.2	>= 1.5
82	3.2	>= 1.5
215	3.2	>= 1.5

[B] Inhibiting activity against COX-I and COX-II (Whole Blood Assay):

(i) Test Method:

Whole blood assay for COX-I

Fresh blood was collected by syringe without anticoagulants from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection. 500μl aliquots of human whole blood were immediately incubated with 2μl of either

DMSO vehicle or a test compound at final concentrations for 1hr at 37C to allow the blood to clot. Appropriate treatments (no incubation) were used as blanks. At the end of the incubation, 5μl of 250mM Indomethacin was added to stop the reaction. The blood was centrifuged at 6000 x g for 5min at 4°C to obtain serum. A 100μl aliquot of serum was mixed with 400μl methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000 x g for 5min at 4°C and was assayed for TXB2 using an enzyme immunoassay kit according to the manufacturer's procedure. For a test compound, the results were expressed as percent inhibition of TXB2 production relative to control incubations containing DMSO vehicle. The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC50 value was calculated by least squares method.

Whole blood assay for COX-II

Fresh blood was collected in heparinized tubes by syringe from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection. 500μl aliquots of human whole blood were incubated with either 2μl DMSO vehicle or 2μl of a test compound at final concentrations for 15min at 37°C . This was followed by incubation of the blood with 10 μl of 5mg/ml lipopolysaccharide for 24hr at 37°C for induction of COX-2. Appropriate PBS treatments (no LPS) were used as blanks. At the end of the incubation, the blood was centrifuged at 6000 x g for 5min at 4°C to obtain plasma. A 100μl aliquot of plasma was mixed with 400μl methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000 x g for 5min at 4°C and was assayed for PGE2 using a radioimmunoassay kit after conversion of PGE2 to its methyl oximate derivative according to the manufacturer's procedure. For a test compound, the results were expressed as percent inhibition of PGE2 production relative to control incubations containing DMSO

vehicle. The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC50 value was calculated by least squares method.

(ii) Test Results:

Test Compound (Example No.)	COX-I IC50 (μM)	COX-II IC50 (μM)
33	< 0.01	> 0.1
34	< 0.01	> 0.1
36	< 0.01	> 0.1
37	< 0.01	> 0.1
43	< 0.01	> 0.1
48	< 0.01	> 0.1
49	< 0.01	> 0.1
54	< 0.01	> 0.1
56	< 0.01	> 0.1
60	< 0.01	> 0.1
62	< 0.01	> 0.1
63	< 0.01	> 0.1
64	< 0.01	> 0.1
77	< 0.01	> 0.1
82	< 0.01	> 0.1
215	< 0.01	> 0.1

It appeared, from the above-mentioned Test Results, that the compound (I) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting activity against COX, particularly a selective inhibiting activity against COX-I.

Additionally, it was further confirmed that the compounds (I) of the present invention lack undesired side-effects of non-selective NSAIDs, such as gastrointestinal disorders, bleeding, renal toxicity, cardiovascular affection, etc.

The object compound (I) or pharmaceutically acceptable salts thereof of this invention possesses COX inhibiting activity and possesses strong anti-inflammatory, antipyretic, analgesic, antithrombotic, anti-cancer activities, and so on.

The object compound (I) and pharmaceutically acceptable salt thereof, therefore, are useful for treating and/or preventing COX mediated diseases, inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunological diseases, thrombosis, cancer and neurodegenerative diseases in human beings or animals by using administered systemically or topically.

More particularly, the object compound (I) and pharmaceutically acceptable salts thereof are useful for treating and/or preventing inflammation and acute or chronic pain in joint and muscle [e.g. rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, scapulohumeral periarthritis, cervical syndrome, etc.]; lumbago;
inflammatory skin condition [e.g. sunburn, burns, eczema, dermatitis, etc.];
inflammatory eye condition [e.g. conjunctivitis, etc.];
lung disorder in which inflammation is involved [e.g. asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.];
condition of the gastrointestinal tract associated with inflammation [e.g. aphthous ulcer, Chrohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.]; gingivitis; menorrhalgia;
inflammation, pain and tumescence after operation or injury [pain after odontectomy, etc] ;
pyrexia, pain and other conditions associated with inflammation, particularly those in which lipoxygenase and cyclooxygenase products are a factor,
systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodose, rheumatic fever,

Sjogren's syndrome, Behcet disease, thyroiditis, type I diabetes, nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimers disease, or the like.

Additionally, the object compound (I) or a salt thereof is expected to be useful as therapeutical and/or preventive agents for cardiovascular or cerebrovascular diseases, the diseases caused by hyperglycemia and hyperlipemia.

The object compound (I) and a salt thereof can be used for prophylactic and therapeutic treatment of arterial thrombosis, arterial sclerosis, ischemic heart diseases [e.g. angina pectoris (e.g. stable angina pectoris, unstable angina pectoris including imminent infarction, etc.), myocardial infarction (e.g. acute myocardial infarction, etc.), coronary thrombosis, etc.], ischemic brain diseases [e.g. cerebral infarction (e.g. acute cerebral thrombosis, etc.), cerebral thrombosis (e.g. cerebral embolism, etc.), transient cerebral ischemia (e.g. transient ischemic attack, etc.), cerebrovascular spasm after cerebral hemorrhage (e.g. cerebrovascular spasm after subarachnoid hemorrhage, etc.), etc.], pulmonary vascular diseases (e.g. pulmonary thrombosis, pulmonary embolism etc.), peripheral circulatory disorder [e.g. arteriosclerosis obliterans, thromboangiitis obliterans (i.e. Buerger's disease), Raynaud's disease, complication of diabetes mellitus (e.g. diabetic angiopathy, diabetic neuropathy, etc.), phiebothrombosis (e.g. deep vein thrombosis, etc.), etc.], complication of tumors (e.g. compression thrombosis), abortion [e.g. placental thrombosis, etc.], restenosis and reocclusion [e.g. restenosis and/or reocclusion after percutaneous transluminal coronary angioplasty (PTCA), restenosis and reocclusion after the administration of thrombolytic drug (e.g. tissue plasminogen activator (TPA), etc.)], thrombus formation in case of vascular surgery, valve replacement, extracorporeal circulation [e.g. surgery (e.g. open heart surgery,

pump-oxygenator, etc.) hemodialysis, etc.] or transplantation, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenia, essential thrombocytosis, inflammation (e.g. nephritis, etc.), immune diseases, atrophic thrombosis, creeping thrombosis, dilation thrombosis, jumping thrombosis, mural thrombosis, etc.

The object compound (I) and a salt thereof can be used for the adjuvant therapy with thrombolytic drug (e.g. TPA, etc.) or anticoagulant (e.g. heparin, etc.).

And, the compound (I) is also useful for inhibition of thrombosis during extra corporeal circulation such as dialysis.

Particularly, the following diseases are exemplified: pains caused by or associated with rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid spondylitis, gouty arthritis, juvenile arthritis, etc; lumbago; cervico-omo-brachial syndrome; scapulohumeral periarthritis; pain and tumescence after operation or injury; etc.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting, or emulsifying agents, buffers and other commonly used additives.

While the dosage of therapeutically effective amount of the compound (I) will vary depending upon the age and condition of each individual patient, an average single dose of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000

mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.01 mg/body and about 1,000 mg/body may be administered per day.

For therapeutic purpose, the analgesic agent of the present invention can be used in a form of pharmaceutical preparation suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like.

Particularly, the analgesic agent of this invention is useful for treating or preventing acute or chronic pains associated with acute or chronic inflammations in human beings or animals by using administered systemically or topically.

(continued to the next page)

In the above and subsequent description of the present specification, the following abbreviations and acronyms mean ones as shown in the following table.

Abbreviations and Acronyms	Full Name
AcOEt or EtOAc	ethyl acetate
AcOH	acetic acid
BuOH, t-BuOH, etc.	butanol, t-butyl alcohol, etc.
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
Et3N	triethylamine
EtOH	ethanol
IPE	diisopropyl ether
MeOH	methanol
PrOH, i-PrOH or IPA, etc.	propanol, isopropyl alcohol, etc.
TFA	trifluoroacetic acid
THF	tetrahydrofuran
EDCI or WSCD	1-ethyl-3-[3'-(dimethylamino)propyl]carbodiimide
HOBt or HOBT	1-hydroxybenztriazole
Pd/C	palladium on carbon
MCBA or mCPBA or mcpba	3-Chloroperoxybenzoic acid
deg	°C=degree centigrade
min	minute(s)
hr or h	hour(s)
conc.	concentrated
aq	aqueous (ex. aq NaHCO3 solution)

The following Examples and Preparations are given only for the purpose of illustrating the present invention in more detail.

Preparation 1

N^1-(4-Benzyloxyphenyl)-4-methoxybenzamidine (P0001)

To a solution of 4-benzyloxyaniline hydrochloride (3g) in tetrahydrofuran (15ml), 1.0M sodium bis(trimethylsilyl)amide in tetrahydrofuran (26.7ml) was added dropwise at room temperature. After the mixture was stirred for 20min, anisonitrile (1.69g) was added.

The reaction mixture was stirred for 4hrs, and then poured into 300ml of ice-water. The precipitate was collected by filtration, washed with diisopropyl ether to give the target compound (3.3g).

1H NMR (200MHz, DMSO-d_6, δ) : 3.8(3H, s), 5.05(2H, s), 6.09(2H, bs), 6.74-6.8(2H, m), 6.96(4H, d, J=8.5Hz), 7.29-7.49(5H, m), 7.92(2H, d, J=8.9Hz).
MS m/e : 333 $(M+H)^+$.

Preparation 2

4-Cyano-4,5-dihydro-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole (P0002)

A mixture of N^1-(4-Benzyloxyphenyl)-4-methoxybenzamidine obtained by Preparation 1 (2g), 2-chlorocyanoethylene (0.36ml) and N,N-diisopropylethylamine (0.79ml) in tetrahydrofuran (10ml) was stirred at reflux condition overnight.

After cooling to room temperature, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and brine, then dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica-gel column chromatography eluting with (n-Hexane:Ethyl acetate=1:1)to give the target compound (0.82g).

MP : 121-122℃.

1H NMR (200MHz, DMSO-d_6, δ) : 3.74(3H, s), 4.11-4.19(2H, m),

5.03(2H, s), 5.16-5.25(1H, m), 6.87(2H, d, J=9Hz), 6.93(4H, s), 7.29-7.44(7H, m).
MS (ESI$^+$) m/e : 384 $(M+H)^+$.

Preparation 3

4-Cyano-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole (P0003)

A suspension of 4-cyano-4,5-dihydro-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Preparation 2 (0.8g) and manganese(IV) oxide (0.91g) in N,N-dimethylformamide (8ml) was stirred at 100℃ for 4hrs.

After filtration, the reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. To the solution of the residue in N,N-dimethylformamide (8ml), phosphorus oxychloride (0.58ml) was added under stirring at 0℃.

After stirring at room temperature for 2hrs, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica-gel column chromatography eluting with (n-Hexane:Ethyl acetate=3:1 to 1:1) to give the target compound (0.74g) as an oil.

1H NMR (200MHz, DMSO-d_6, δ) : 3.75(3H, s), 5.16(2H, s), 6.89(2H, d, J=8.5Hz), 7.12(2H, d, J=9Hz), 7.25-7.48(9H, m), 8.4(1H, s).
MS (ESI$^+$) m/e : 382 $(M+H)^+$.

Preparation 4

1-(4-Benzyloxyphenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole (P0004)

A mixture of N^1-(4-Benzyloxyphenyl)-4-methoxybenzamidine (1g), 3-bromo-1,1,1-trifluoropropanone (0.47ml) and sodium hydrogencarbonate (506mg) in isopropyl alcohol (10ml) was stirred

at reflux condition overnight.

After cooling to room temperature, the reaction mixture was filtrated and evaporated in vacuo. Then the residue was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica-gel column chromatography eluting with (n-Hexane:Ethyl acetate=1:1) to give the target compound (0.55g) as an oil.

1H NMR (DMSO-d_6, δ) : 3.75(3H, s), 5.16(2H, s), 6.86-6.92(2H, m), 7.09-7.13(2H, m), 7.25-7.50(9H, m), 8.08(1H, d, J=1.4Hz).
IR (Neat, cm^{-1}) : 3120, 3068, 2973, 2843, 1610.
MS m/e : 425 (M^++1).

Preparation 5

1-(4-Hydroxyphenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole (P0005)

1-(4-Benzyloxyphenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole obtained by Preparation 4 (0.55g) and dry 20% $Pd(OH)_2/C$ (200mg) in ethanol (10ml) and cyclohexene (5ml) was stirred at reflux condition for 2hrs and cooled to room temperature.

After filtration, the reaction mixture was evaporated in vacuo to give the target compound (0.44g).

MP : 215-216℃.
1H NMR (DMSO-d_6, δ) : 3.74(3H, s), 6.81-6.92(4H, m), 7.16-7.30(4H, m), 8.03(1H, d, J=1.3Hz).
IR (KBr, cm^{-1}) : 3149, 3103, 3037, 2964, 2910, 2829, 2690, 2611, 1649, 1614.
MS m/e : 335 (M^++1).

Preparation 6

1-(4-Hydroxyphenyl)-2-(2-methoxy-5-pyridyl)-4-trifluoromethyl-1H-imidazole (P0006)

To a solution of 1-(4-benzyloxyphenyl)-2-(2-methoxy-5-pyridyl)-4-trifluoromethyl-1H-imidazole obtained by Preparation 13 (2.25g, 5.29mmol) in cyclohexene (22ml) and ethanol (45ml) was added 20% palladium hydroxide on carbon (550mg). The resulting mixture was stirred at reflux for 2hrs.

After cooling to room temperature, the mixture was filtered through Celite and washed with ethanol. The filtrate was concentrated in vacuo, and then the residue was washed with diisopropyl ether to give 1.31g of desired compound as a white solid (73.9%).

MP : 198-200℃.

IR (KBr, cm^{-1}) : 3600-2600, 1469, 1292, 1247, 1159, 1126, 833.

NMR ($CDCl_3$, δ) : 3.91(3H, s), 6.67(1H, brs), 6.73(1H, d, J=9Hz), 6.87(2H, d, J=9Hz), 7.11(2H, d, J=9Hz), 7.43(1H, s), 7.86(1H, dd, J=9Hz and 2Hz), 8.03(1H, d, J=2Hz).

MS : 336 $(M+H)^+$.

Preparation 7

4-Ethoxycarbonyl-4,5-dihydro-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole (P0007)

A mixture of N^1-(4-benzyloxyphenyl)-4-methoxybenzamidine (1.25g), ethyl 2-chloroacrylate (0.76g) and N,N-diisopropylethylamine (0.98ml) in tetrahydrofuran (12ml) was stirred at reflux condition for 2hrs.

After cooling to room temperature, the reaction mixture was filtered off and the filtrate was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo.

This material was used in the next step without further purification.

Preparation 8

4-Ethoxycarbonyl-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole (P0008)

The residue of Preparation 7 was dissolved in N,N-dimethylformamide (10ml), and manganese(IV) oxide (1.63g) was added to the solution.

After stirring at 100℃ for 4hrs, the reaction mixture was cooled to room temperature and poured into water and ethyl acetate. After filtration, the mixture was extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 1.5g of desired compound as an oil (93.1%).

IR (Neat, cm^{-1}) : 3433, 3253, 3224, 3140, 3064, 2966, 2843, 1722, 1712, 1606.

NMR (DMSO-d_6, δ) : 1.29(3H, t, J=7.1Hz), 3.75(3H, s), 4.27(2H, d, J=7.1Hz), 5.15(2H, s), 6.88(2H, dt, J=8.9Hz and 1.9Hz), 7.10(2H, dt, J=8.9Hz and 1.9Hz), 7.24-7.49(9H, m), 8.04(1H, s).

MS : 429 $(M+H)^+$.

Preparation 9

1-(4-Benzyloxyphenyl)-4-formyl-2-(4-methoxyphenyl)-1H-imidazole (P0009)

0.95N Diisopropyl alminium hydride in toluene (6.49ml) was added dropwise to a solution of 4-ethoxycarbonyl-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Preparation 8 (0.88g) in dichloromethane (5ml) under stirring at -78℃, and stirred at -78℃ for 2hrs.

The reaction mixture was quenched by sat. ammonium chloride aq., then 1N hydrochloric acid was added and extracted with water. After sodium hydroxide aq. was added, extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo.

The residue was dissolved in N,N-dimethylformamide (10ml), and manganese(IV) oxide (1.79g) was added to the solution.

After stirring at 100℃ for 1hr, the reaction mixture was

cooled to room temperature and poured into water and ethyl acetate. After filtration, the mixture was extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 0.77g of desired compound as an oil (97.5%).

IR (Neat, cm^{-1}) : 3440, 3361, 3219, 3124, 3062, 2937, 2837, 2760, 1732, 1684, 1610.

NMR (DMSO-d_6, δ) : 3.75(3H, s), 5.16(2H, s), 6.89(2H, dt, J=8.9Hz and 1.9Hz), 7.12(2H, dt, J=8.9Hz and 2.1Hz), 7.27-7.49(9H, m), 8.28(1H, s), 9.82(1H,s).

MS : 385 $(M+H)^+$.

Preparation 10

1-(4-Benzyloxyphenyl)-4-difluoromethyl-2-(4-methoxyphenyl)-1H-imidazole (P0010)

Diethylaminosulfur trifluoride (0.46 ml) was added to a solution of 1-(4-benzyloxyphenyl)-4-formyl-2-(4-methoxyphenyl)-1H-imidazole obtained by Preparation 9 (0.45g) in dichloromethane (5ml) under stirring at 0℃.

After stirring at room temperature for overnight, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 0.38g of desired compound as an oil (79.9%).

IR (Neat, cm^{-1}) : 3433, 3155, 3113, 3066, 3041, 2964, 2841, 1732, 1610.

NMR (DMSO-d_6, δ) : 3.74(3H, s), 5.15(2H, s), 6.87(2H, d, J=8.9Hz), 7.08(1H, t, J=55.0Hz), 7.10(2H, d, J=8.9Hz), 7.24-7.45(9H, m), 7.73(1H, t, J=2.3Hz).

MS : 407 $(M+H)^+$.

Preparation 11

4-Difluoromethyl-1-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole (P0011)

A suspension of 1-(4-benzyloxyphenyl)-4-difluoromethyl-2-(4-methoxyphenyl)-1H-imidazole obtained by Preparation 10 (0.38g) and dry 20% palladium hydroxide on carbon ($Pd(OH)_2/C$) (100mg) in ethanol (8ml) and cyclohexene (4ml) was stirred at reflux condition for 1hr and cooled to room temperature.

After filtration, the reaction mixture was evaporated in vacuo to give 0.3g of desired compound (ca.100%).

MP : 143-145℃

IR (KBr, cm^{-1}) : 3149, 3111, 3003, 2966, 2837, 2804, 2679, 2602, 1610.

NMR (DMSO-d_6, δ) : 3.74(3H, s), 6.80-6.91(4H, m), 6.96(1H, t, J=55.0Hz), 7.14(2H, dt, J=8.7Hz and 1.9Hz), 7.27(2H, dt, J=8.9Hz and 1.9Hz), 7.68(1H, t, J=2.2Hz), 9.90(1H, s).

MS : 317 $(M+H)^+$.

Preparation 12

N^1-(4-Benzyloxyphenyl)-2-methoxy-5-amidinopyridine (P0012)

Reaction was carried out in a manner similar to Preparation 1 using 4-benzyloxyaniline hydrochloride to give 8.7g of desired compound (71.7%).

IR (KBr, cm^{-1}) : 3488, 3396, 3031, 2958, 1635, 1502, 1373, 1236, 1103, 1020, 840.

NMR (DMSO-d_6, δ) : 3.90(3H, s), 5.06(2H, s), 6.28(2H, brs), 6.70-7.05(5H, m), 7.25-7.60(5H, m), 8.24(1H, dd, J=9Hz and 2Hz), 8.72(1H, d, J=2Hz).

MS : 334 $(M+H)^+$.

Preparation 13

1-(4-Benzyloxyphenyl)-2-(2-methoxy-5-pyridyl)-4-trifluoromethyl-1H-imidazole (P0013)

Reaction was carried out in a manner similar to Preparation 4 using N^1-(4-Benzyloxyphenyl)-2-methoxy-5-amidinopyridine obtained by Preparation 12 to give 2.27g of desired compound (44.5%).

IR (KBr, cm^{-1}) : 3064, 2950, 1290, 1244, 1157, 1122, 1022, 835.
NMR (DMSO-d_6, δ) : 3:84(3H, s), 5.16(2H, s), 6.81(1H, d, J=9Hz), 7.05-7.58(9H, m), 7.65(1H, dd, J=9Hz and 2Hz), 8.08(1H, d, J=2Hz), 8.17(1H, s).
MS : 426 $(M+H)^+$.

Preparation 14

1-(4-Benzyloxyphenyl)-4,5-dihydro-4-ethoxycarbonyl-2-(2-methoxy-5-pyridyl)-1H-imidazole (P0014)

2.67g of desired compound was obtained from a mixture of N^1-(4-benzyloxyphenyl)-2-methoxy-5-amidinopyridine (2.57g) and ethyl 2-chloacrylate (1.56g) in the similar manner to that of Preparation 7 (80.3%).

IR (Neat, cm^{-1}) : 3448, 3411, 3378, 3037, 2981, 2949, 2902, 1734, 1608.
NMR (DMSO-d_6, δ) : 1.24(3H, t, J=7.1Hz), 3.83(3H, s), 4.06(2H, d, J=9.9Hz), 4.17(2H, q, J=7.1Hz), 4.81(1H, t, J=9.8Hz), 5.04(2H, s), 6.77(1H, d, J=8.6Hz), 6.93(4H, s), 7.29-7.44(5H, m), 7.68(1H, dd, J=8.6Hz and 2.4Hz), 8.18(1H, d, J=2.4Hz).
MS : 432 $(M+H)^+$.

Preparation 15

1-(4-Benzyloxyphenyl)-4-ethoxycarbonyl-2-(2-methoxy-5-pyridyl)-1H-imidazole (P0015)

1.74g of desired compound was obtained from a suspension of 1-(4-benzyloxyphenyl)-4,5-dihydro-4-ethoxycarbonyl-2-(2-methoxy-5-pyridyl)-1H-imidazole obtained by Preparation 14 (2.67g) in N,N-dimethylformamide (27ml) in the similar manner to that of Preparation 8 (65.5%).

MP : 109-110℃.
IR (KBr, cm^{-1}) : 3433, 3390, 3136, 3070, 2976, 2941, 2841, 1693, 1608.
NMR (DMSO-d_6, δ) : 1.29(3H, t, J=7.1Hz), 3.84(3H, s), 4.28(2H, q, J=7.1Hz), 5.15(2H, s), 6.80(1H, d, J=8.6Hz), 7.12(2H, d, J=8.9Hz), 7.32-7.49(7H, m), 7.65(1H, dd, J=8.6Hz and 2.4Hz), 8.06(1H, d, J=2.4Hz), 8.12(1H, s).
MS : 430 $(M+H)^+$.

Preparation 16

1-(4-Benzyloxyphenyl)-4-formyl-2-(2-methoxy-5-pyridyl)-1H-imidazole (P0016)

0.83g of desired compound was obtained from 1-(4-benzyloxyphenyl)-4-ethoxycarbonyl-2-(2-methoxy-5-pyridyl)-1H-imidazole (1.46g) in the similar manner to that of Preparation 9 (63.3%).

IR (Neat, cm^{-1}) : 3217, 3126, 3059, 2947, 2831, 2760, 1687, 1606.
NMR (DMSO-d_6, δ) : 3.84(3H, s), 5.16(2H, s), 6.82(1H, d, J=8.5Hz), 7.14(2H, dt, J=8.9Hz and 2.0Hz), 7.35-7.50(7H, m), 7.66(1H, dd, J=8.6Hz and 2.5Hz), 8.11(1H, d, 2.3Hz), 8.35(1H, s), 9.84(1H, s).
MS : 386 $(M+H)^+$.

Preparation 17

1-(4-Benzyloxyphenyl)-4-difluoromethyl-2-(2-methoxy-5-pyridyl)-1H-imidazole (P0017)

0.48g of desired compound was obtained from

1-(4-benzyloxyphenyl)-4-formyl-2-(2-methoxy-5-pyridyl)-1H-imidazole obtained by Preparation 16 (0.83g) in the similar manner to that of Preparation 10 (54.7%).

IR (Neat, cm^{-1}) : 3429, 3209, 3151, 3064, 3028, 2979, 2949, 2875, 2549, 1734, 1604.
NMR (DMSO-d_6, δ) : 3.84(3H, s), 5.15(2H, s), 6.80(1H, d, J=8.5Hz), 7.00(1H, t, J=54.8Hz), 7.12(2H, d, J=9.0 Hz), 7.27-7.49(7H, m), 7.63(1H, dd, J=8.6Hz and 2.5Hz), 7.81(1H, t, J=2.2Hz), 8.07(1H, d, J=1.8Hz).
MS : 408 $(M+H)^+$.

Preparation 18

4-Difluoromethyl-1-(4-hydoxyphenyl)-2-(2-methoxy-5-pyridyl)-1H-imidazole (0018)

0.48g of desired compound was obtained from 1-(4-benzyloxyphenyl)-4-difluoromethyl-2-(2-methoxy-5-pyridyl)-1H-imidazole obtained by Preparation 17 (0.48 g) in the similar manner to that of Preparation 6 (ca.100%).

MP : 155-156℃.
IR (KBr, cm^{-1}) : 3012, 2962, 2808, 2681, 2603, 1603.
NMR (DMSO-d_6, δ) : 3.83(3H, s), 6.77-6.86(3H, m), 6.99(1H, t, J=54.9Hz), 7.19(2H, d, J=8.8Hz), 7.63(1H, dd, J=8.7Hz and 2.5Hz), 7.76(1H, t, J=2.2Hz), 8.06(1H, d, J=2.4Hz), 10.06(1H, br).
MS : 318 $(M+H)^+$.

Preparation 19

1-(4-Benzyloxyphenyl)-4-cyano-4,5-dihydro-2-(2-methoxy-5-pyridyl)-1H-imidazole (P0019)

The target compound was obtained from N^1-(4-Benzyloxyphenyl)- 2-methoxy-5-pyridylamidine in the similar manner to that of Preparation 2.

1H NMR (200MHz, DMSO-d_6, δ) : 3.84(3H, s), 4.15-4.21(2H, m), 5.05(2H, s), 5.25(1H, dd, J=8.8, 10.5Hz), 6.78(1H, d, J=8.5Hz), 6.92-7.04(4H, m), 7.32-7.45(5H, m), 7.66(1H, dd, J=2.5, 8.5Hz), 8.19(1H, d, J=2Hz).

MS (ESI^+) m/e : 385 $(M+H)^+$.

Preparation 20

1-(4-Benzyloxyphenyl)-4-cyano-2-(2-methoxy-5-pyridyl)-1H-imidazole (P0020)

The target compound was obtained from 1-(4-Benzyloxyphenyl)-4-cyano-4,5-dihydro-2-(2-methoxy-5-pyridyl)-1H-imidazole obtained by Preparation 19 in the similar manner to that of Preparation 3.

1H NMR (200MHz, DMSO-d_6, δ) : 3.84(3H, s), 5.16(2H, s), 6.81(1H, d, J=8Hz), 7.14(2H, d, J=9Hz), 7.316-7.5(7H, m), 7.63(1H, dd, J=2.3, 8.5Hz), 8.1(1H, dd, J=2.5Hz), 8.47(1H, s).

MS (ESI^+) m/e : 383 $(M+H)^+$.

Preparation 21

1-(4-Benzyloxyphenyl)-4-isopropylcarbonyl-2-(2-methoxy-5-pyridyl)-1H-imidazole (P0021)

The target compound (1.04g) was obtained from 1-(4-benzyloxyphenyl)-4-cyano-2-(2-methoxy-5-pyridyl)-1H-imidazole obtained by Preparation 20 in the similar manner to that of Preparation 23.

MP : 118-120℃.

1H NMR (DMSO-d_6, δ) : 1.14(6H,d, J=6.8Hz), 3.56-3.70(1H, m), 3.84(3H, s), 5.16(2H, s), 6.81(1H, d, J=8.5Hz), 7.13(2H, dd, J=9.1Hz, 2.3Hz), 7.32-7.49(7H, m), 7.67(1H, dd, J=8.5Hz, 2.4Hz), 8.08(1H, d, J=2.4Hz), 8.19(1H, s).

IR (KBr, cm^{-1}) : 3126, 3064, 3033, 2968, 2875, 1660, 1608.

MS m/e : 428 (M^++1).

Preparation 22

4-Isopropylcarbonyl-1-(4-hydroxyphenyl)-2-(2-methoxy-5-pyridyl)-1H-imidazole (P0022)

The target compound was obtained from 1-(4-benzyloxyphenyl)-4-isopropylcarbonyl-2-(2-methoxy-5-pyridyl)-1H-imidazole obtained by Preparation 21 in the similar manner to that of Preparation 5.

MP : 185-187℃.

1H NMR (DMSO-d_6, δ) : 1.14(6H,d, J=6.8Hz), 3.56-3.69(1H, m), 3.84(3H, s), 6.79-6.86(3H, m), 7.17-7.25(2H, m), 7.67(1H, dd, J=8.8Hz, 2.4Hz), 8.07(1H, d, J=2.4Hz), 8.14(1H, s), 9.98(1H, s).

IR (KBr, cm^{-1}) : 3134, 2972, 2891, 2812, 2744, 2681, 2607, 1676, 1612.

MS m/e : 338 (M^++1).

Preparation 23

1-(4-Benzyloxyphenyl)-4-ethylcarbonyl-2-(2-methoxy-5-pyridyl)-1H-imidazole (P0023)

To a solution of 1-(4-benzyloxyphenyl)-4-cyano-2-(2-methoxy- 5-pyridyl)-1H-imidazole obtained by Preparation 20 (1.1g) in tetrahydrofuran (10ml), 1N solution of ethylmagnesium bromide in tetrahydrofuran (8.63ml) was added under stirring at 0℃.

After stirring at room temperature for 1hr, the reaction mixture was poured into aqueous 10% potassium hydrogen sulfate and stirred at room temperature for 30min. The mixture was alkalinized with saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, washed with water, dried over magnesium sulfate and evaporated in vacuo. The resulting precipitates were collected by filtration and washed with

diisopropyl ether to give the target compound (1.07g).

MP : 126-128℃.

1H NMR (DMSO-d_6, δ) : 1.10(3H, t, J=7.4Hz), 2.95(2H, q, J=7.4Hz), 3.84(3H, s), 5.16(2H, s), 6.81(1H, d, J=8.6Hz), 7.12(2H, d, J=8.9Hz), 7.32-7.49(7H, m), 7.66(1H, dd, J=8.6Hz, 2.4Hz), 8.08(1H, d, J=2.4Hz), 8.17(1H, s).

IR (KBr, cm^{-1}) : 3217, 3126, 3066, 3030, 2972, 2939, 2883, 1666, 1610.

MS m/e : 414 (M^++1).

Preparation 24

4-Ethylcarbonyl-1-(4-hydroxyphenyl)-2-(2-methoxy-5-pyridyl)-1H-imidazole (P0024)

The target compound was obtained from 1-(4-benzyloxyphenyl)-4- ethylcarbonyl-2-(2-methoxy-5-pyridyl)-1H-imidazole obtained by Preparation 23 in the similar manner to that of Preparation 5.

MP : 221-223℃.

1H NMR (DMSO-d_6, δ) : 1.10(3H, t, J=7.3Hz), 2.95(2H, q, J=7.3Hz), 3.84(3H, s), 6.79-6.88(3H, m), 7.20(2H, dt, J=9.6 Hz, 2.7Hz), 7.66(1H, dd, J=8.7Hz, 2.4Hz), 8.07(1H, d, J=2.4Hz), 9.97(1H, s).

IR (KBr, cm^{-1}) : 3215, 3136, 3053, 2978, 2947, 2900, 1676, 1603.

MS m/e : 324 (M^++1).

Preparation 25

1-(4-Benzyloxyphenyl)-4-carboxy-2-(4-methoxyphenyl)-1H-imidazole (P0025)

To a solution of 4-ethoxycarbonyl-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Preparation 8 (1.46g) in ethanol (10ml) and tetrahydrofuran (10ml), 1N aqueous

sodium hydroxide (6.81ml) was added.

After stirring at room temperature overnight, the reaction mixture was poured into water and ethyl acetate, and extracted with water. Then, the water layer was acidified with 1N hydrochloric acid, extracted with ethyl acetate, dried over magnesium sulfate, and evaporated in vacuo. The resulting precipitates were collected by filtration and washed with diisopropyl ether to give the target compound (1.1g).

MP : 113-115℃.

1H NMR (200MHz, DMSO-d_6, δ) : 3.75(3H, s), 5.15(2H, s), 6.88(2H, d, J=8.8Hz), 7.10(2H, d, J=8.9Hz), 7.24-7.45(9H, m), 7.96(1H, s), 11.0-12.5(1H, br).

IR (KBr, cm^{-1}) : 3392, 3224, 3145, 3076, 2972, 2935, 2893, 1701, 1610.

Preparation 26

1-(4-Benzyloxyphenyl)-4-(N-ethyl-N-methylcarbamoyl)-2-(4-methoxyphenyl)-1H-imidazole (P0026)

A mixture of 1-(4-benzyloxyphenyl)-4-carboxy-2-(4-methoxyphenyl)-1H-imidazole obtained by Preparation 25 (0.44g), ethylmethylamine (118ml), 1-hydroxybenzotriazole (186mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (263mg) in N,N-dimethylformamide (5ml) was stirred at room temperature overnight.

The reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica-gel column chromatography eluting with (n-Hexane:Ethyl acetate=1:1). The resulting precipitates were corrected by filtration and washed with diisopropyl ether to give the target compound (0.44g).

MP : 118-119℃.

1H NMR (DMSO-d_6, δ) : 1.06-1.28(3H, m), 2.91-3.02(2H, m),

3.40-3.54(2H, m), 3.74(3H, s), 3.93-4.07(1H, m), 5.15(2H, s), 6.88(2H, d, J=8.8Hz), 7.10(2H, d, J=8.9Hz), 7.24-7.30(4H, m), 7.36-7.49(5H, m), 7.73(1H, s).

IR (KBr, cm^{-1}): 3124, 3066, 2958, 2935, 2839, 1608.

Mass m/e : 442 (M^++1).

Preparation 27

4-(N-Ethyl-N-methylcarbamoyl)-1-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole (P0027)

The target compound was obtained from 1-(4-benzyloxyphenyl)-4-(N-ethyl-N-methylcarbamoyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Preparation 26 in the similar manner to that of Preparation 5.

1H NMR (DMSO-d_6, δ) : 1.10-1.28(3H, m), 2.90-3.02(2H, m), 3.40-3.50(2H, m), 3.74(3H, s), 3.91-4.03(1H, m), 6.82(2H, d, J=8.7Hz), 6.88(2H, d, J=8.9Hz), 7.11(1H, s), 7.14(2H, d, J=8.7Hz), 7.27(2H, d, J=8.7Hz), 7.67(1H, s).

IR (KBr, cm^{-1}) : 3126, 3091, 3018, 2968, 2933, 2831, 2738, 2677, 2600, 2476, 1612.

MS m/e : 352 (M^++1).

Preparation 28

1-(4-Benzyloxyphenyl)-4-(N,N-diethylcarbamoyl)-2-(4-methoxy-phenyl)-1H-imidazole (P0028)

The target compound was obtained from 1-(4-benzyloxyphenyl)-4-carboxy-2-(4-methoxyphenyl)-1H-imidazole obtained by Preparation 25 and N,N-diethylamine in the similar manner to that of Preparation 26.

MP : 146-147℃.

1H NMR (DMSO-d_6, δ) : 1.10-1.30(6H, m), 3.38-3.50(2H, m), 3.74(3H, s), 3.85-4.02(2H, m), 5.15(2H, s), 6.88(2H, d, J=8.8Hz), 7.10(2H, d, J=8.9Hz), 7.24-7.30(4H, m), 7.36-7.49(5H, m), 7.72(1H, s).

IR (KBr, cm^{-1}) : 3113, 2972, 2929, 1593.
MS m/e : 456 (M^++1).

Preparation 29

4-(N,N-Diethylcarbamoyl)-1-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole (P0029)

The target compound was obtained from 1-(4-benzyloxyphenyl)-4-(N,N-diethylcarbamoyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Preparation 28 in the similar manner to that of Preparation 5.

1H NMR (DMSO-d_6, δ) : 1.02-1.30(6H, m), 3.22-3.48(2H, m), 3.73(3H, s), 3.83-4.02(2H, m), 6.81-6.92(4H, m), 7.14(2H, dd, J=6.7Hz, 2.0Hz), 7.27(2H, dt, J=9.4Hz, 2.5Hz), 7.66(1H, s).
IR (KBr, cm^{-1}) : 3145, 3030, 2970, 2937, 2833, 1693, 1606.
MS m/e : 366 (M^++1).

Preparation 30

1-(4-Benzyloxyphenyl)-2-(4-methoxyphenyl)-4-(1-piperidinecarbonyl)-1H-imidazole (P0030)

The target compound (0.5g) was obtained from 1-(4-benzyloxyphenyl)-4-carboxy-2-(4-methoxyphenyl)-1H-imidazole obtained by Preparation 25 and piperidine in the similar manner to that of Preparation 26.

1H NMR (200MHz, DMSO-d_6, δ) : 1.507-1.572(4H, m), 1.605-1.67(2H, m), 3.462-3.644(2H, m), 3.74(3H, s), 3.918-4.244(2H, m), 5.144(2H, s), 6.879(2H, d, J=4.5Hz), 7.096(2H, d, J=4.5Hz), 7.251(2H, d, J=4.3Hz), 7.278(2H, d, J=4.3Hz), 7.348-7.478(5H, m), 7.721(1H, s).
IR (KBr, cm^{-1}) : 3116, 3033, 2931, 2850.
MS m/e : 468 $(M+H)^+$.

Preparation 31

1-(4-Hydroxyphenyl)-2-(4-methoxyphenyl)-4-(1-piperidine-carbonyl)-1H-imidazole (P0031)

The target compound (0.41g) was obtained from 1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-4-(1-piperidine-carbonyl)-1H-imidazole obtained by Preparation 30 in the similar manner to that of Preparation 5.

1H NMR (200MHz, DMSO-d_6, δ) : 1.509-1.577(4H, m), 1.611-1.674(2H, m), 3.51-3.657(2H, m), 3.734(3H, s), 4.035-4.224(2H, m), 6.814(2H, d, J=4.4Hz), 6.881(2H, d, J=4.3Hz), 7.136(2H, d, J=4.4Hz), 7.256(2H, d, J=4.4Hz), 7.668(1H, s), 9.908(1H, bs).
IR (KBr, cm^{-1}) : 3151, 3035, 2935, 2852, 1606.
MS m/e : 378 $(M+H)^+$.

Preparation 32

4-Cyano-1-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole
(P0032)

The target compound was obtained from 4-cyano-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Preparation 3 in the similar manner to that of Preparation 5.

1H NMR ($CDCl_3$, δ) : 3.74(3H, s), 6.75-6.95(4H, m), 7.10-7.35(4H, m), 8.36(1H, s), 9.98(1H, bs).
MS (ESI, m/e) : 292 (M+1).

Preparation 33

1-(4-Benzyloxyphenyl)-4-cyclopentylcarbonyl-2-(2-methoxy-5-pyridyl)-1H-imidazole (P0033)

To a solution of 1-(4-benzyloxyphenyl)-4-cyano-2-(2-methoxy-5-pyridyl)-1H-imidazole obtained by Preparation 20 (0.8g) in tetrahydrofuran (8ml), 2N solution of

cyclopentylmagnesium chloride in tetrahydrofuran (3.14ml) was added under stirring at 0℃.

After stirring at room temperature for 2hrs, the reaction mixture was poured into aqueous 10% potassium hydrogen sulfate and stirred at room temperature for 30min. The mixture was alkalinized with saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, washed with water, dried over magnesium sulfate and evaporated in vacuo. The resulting precipitates were collected by filtration and washed with diisopropyl ether to give the target compound (0.82g).

1H NMR (200MHz, DMSO-d_6, δ) : 1.57-1.949(m, 8H), 3.764(1H, t, J=7.9Hz), 3.84(3H, s), 5.156(2H, s), 6.81(1H, d, J=8.5Hz), 7.12(2H, d, J=9Hz), 7.328-7.501(7H, m), 7.669(1H, dd, J=8.5Hz, 2.5Hz), 8.078(1H, d, J=1Hz), 8.188(1H, s).
IR (KBr, cm^{-1}) : 3122, 2947, 2868, 1658, 1608.
MS (ESI^+, m/e) : 454 (M+H).

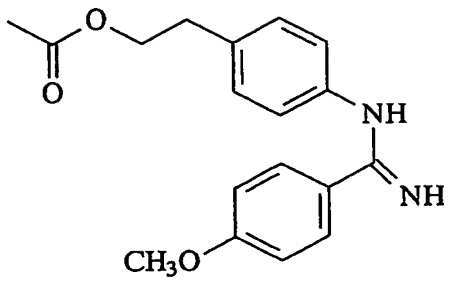
Preparation 34

4-Cyclopentylcarbonyl-1-(4-hydroxyphenyl)-2-(2-methoxy-5-pyridyl)-1H-imidazole (P0034)

The target compound was obtained from 1-(4-Benzyloxyphenyl)-4-cyclopentylcarbonyl-2-(2-methoxy-5-pyridyl)-1H-imidazole obtained by Preparation 33 in the similar manner to that of Preparation 5.

1H NMR (200MHz, DMSO-d_6, δ) : 1.577-1.968(8H, m), 3.761(1H, t, J=8Hz), 3.836(3H, s), 6.793-6.859(3H, m), 7.21(2H, d, J=7Hz), 7.667(1H, dd, J=9Hz, 2.5Hz), 8.069(1H, d, J=1.5Hz), 8.143(1H, s).
IR (KBr, cm^{-1}) : 3220, 3124, 2960, 1674, 1608.
MS (ESI^+, m/e) : 364 (M+H).

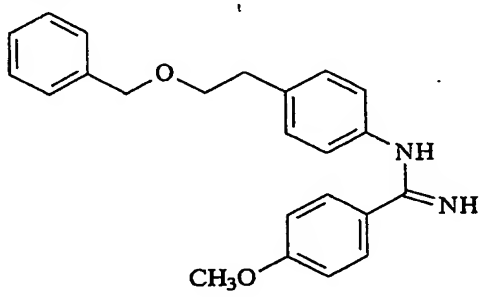
Preparation 35



(P0035)

A mixture of 2-(4-aminophenyl)ethyl acetate (0.3 g), methyl 4-methoxybenzenecarbimidothioate hydroiodide (411 mg) and acetic acid (0.25 ml) in 2-propanol (5 ml) was stirred at reflux condition for 2 hours. After cooling to room temperature, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. Resulting precipitates were corrected by filtration and washed with diisopropyl ether to give P0035 (353 mg).
Mass (ESI^+, m/e): 313 (M^++1)

Preparation 36



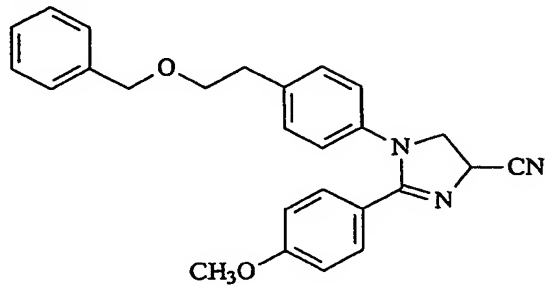
(P0036)

To a solution of 4-(2-benzyloxy)ethyl)aniline (0.5 mg) in tetrahydrofuran (2.5 ml) was added dropwise 1.0M-sodium bis(trimetylsilyl)amide in tetrahydrofuran (2.31 ml) at room temperature. After the mixture was stirred for 20 minutes, anisonitrile (293 mg) was added thereto. The reaction mixture was stirred for 4 hours then poured into ice-water (300 ml). The precipitate was collected by filtration, washed with

diisopropyl ether to give N^1-(4-(2-benzyloxy)ethylphenyl)-4-methoxybenzamidine (P0036) (0.96 g).

Mass (ESI^+, m/e): 361 (M^++1)

Preparation 37



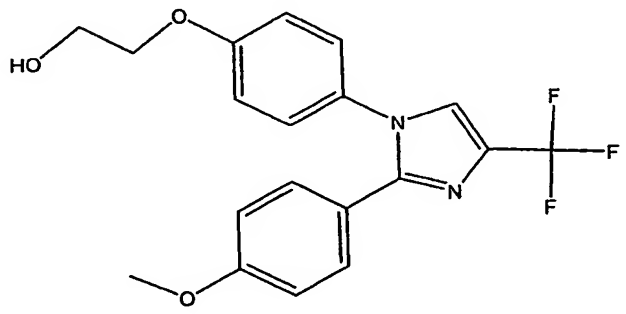
(P0037)

A solution of N^1-(4-(2-benzyloxy)ethylphenyl)-4-methoxybenzamidine (1.3 g), 2-chlorocyanoethylene (0.432 ml) and N,N-diisopropylethylamine (0.942 ml) in tetrahydrofuran (13 ml) was stirred at reflux condition for 4 hours. Additional 2-chlorocyanoethylene (2.01 ml) was added, the mixture was refluxed for overnight. After cooling to room temperature, the reaction mixture was evaporated in vacuo. The residue was purified by column chromatography silica-gel eluting with (n-Hexane:Ethyl acetate=1:1) to give P0037 (1.22g).

NMR (DMSO-d_6) δ; 2.785 (2H, t, J=6.7Hz), 3.597 (2H, t, J=6.7Hz), 3.724 (3H, s), 4.191-4.258 (2H, m), 4.449 (2H, s), 5.216 (1H, dd, J=8.5Hz, 10.5Hz), 6.839 (2H, d, J=6Hz), 6.88 (2H, d, J=6.5Hz), 7.13 (2H, d, J=8Hz), 7.201-7.381 (7H, m)

Mass (ESI^+, m/e): 412 (M^++1)

Example 1



(E0001)

4-[2-(4-Methoxyphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]-phenol (250mg), 2-chloroethanol (0.3ml), potassium carbonate (620 mg) and potassium iodide (745 mg) in N,N-dimethylformamide (1.3ml) was stirred at 75℃ for 6 hours. Then the reaction mixture was poured into water and extracted with ethyl acetate, dried over MgSO4 and evaporated in vacuo.The residue was purified by column chromatography silica-gel eluting with (n-Hexane:Ethyl acetate=1:1) to give (E0001) 2-{4-[2-(4-methoxyphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]-phenoxy}ethanol (0.14 g).

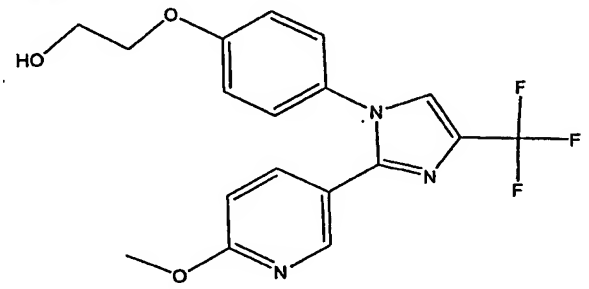
m.p. 149-150℃

NMR (DMSO-d_6) δ; 3.67-3.74 (2H, m), 3.74 (3H, s), 4.03 (2H, t, J=5.3Hz), 4.91 (1H, t, J=5.1Hz), 6.90 (2H, d, J=9.3Hz, 1.9Hz), 7.03 (2H, d, J=8.9Hz), 7.24-7.33 (4H, m), 8.07 (1H, d, J=1.1Hz).

IR (KBr): 3392, 3298, 3111, 3064, 3024, 2951, 2871, 1693, 1610 cm^{-1}.

Mass m/e : 379 (M^++1).

Example 2



(E0002)

2-{4-[2-(2-Methoxypyridin-5-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenoxy}ethanol (E0002) (0.2 g) was obtained from 4-[2-(2-methoxypyridin-5-yl)-4-trifluoromethyl-1H-imidazol-1-yl]phenol (0.21 g) in the similar manner to that of example (E0001).

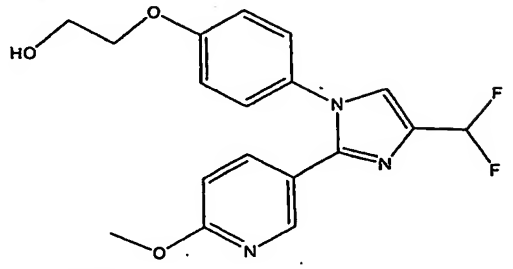
m.p. 89-91℃

NMR (DMSO-d_6) δ; 3.70-7.36 (2H, m), 3.84 (3H, s), 4.04 (2H, t, J=5.0Hz), 4.91 (1H, t, J=5.3Hz), 6.81 (1H, d, J=8.6Hz), 7.05 (2H, d, J=8.9Hz), 7.34-7.07 (2H, m), 7.65 (1H, dd, J=8.6Hz, 2.4Hz), 8.08 (1H, d, J=2.4Hz), 8.16 (1H, d, J=1.4Hz).

IR (KBr): 3381, 3292, 3221, 3113, 3068, 2954, 2871, 1695, 1685, 1651, 1610 cm^{-1}.

Mass m/e : 380 (M^++1).

Example 3



(E0003)

2-{4-[4-(Difluoromethyl)-2-(2-methoxypyridin-5-yl)-1H-imidazol-1-yl]phenoxy}ethanol (E0003) (65 mg) was obtained from 4-[4-difluoromethyl-2-(2-methoxypyridin-5-yl)-1H-imidazol- 1-yl]phenol (0.2 g) in the similar manner to that of E0001.

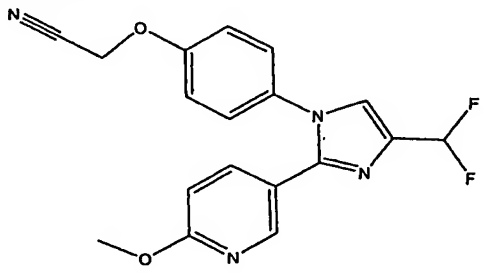
m.p. 72-73℃

NMR (DMSO-d_6) δ; 3.69-3.72 (2H, m), 3.83 (3H, s), 4.90 (1H, t, J=5.4Hz), 6.80 (1H, d, J=8.6Hz), 7.00 (1H, t, J=54.9Hz), 7.00-7.06 (2H, m), 7.28-7.34 (2H, m), 7.63 (1H, dd, J=8.6Hz, 2.4Hz), 7.81 (1H, t, J=2.1Hz), 8.07 (1H, d, J=2.4Hz).

IR (KBr): 3361, 3116, 3068, 3016, 2956, 2873, 1738, 1697, 1687, 1649, 1612 cm^{-1}.

Mass m/e : 362 (M^++1).

Example 4



(E0004)

{4-[4-(Difluoromethyl)-2-(2-methoxypyridin-5-yl)-1H-imidazol-1-yl]phenoxy}acetonitrile (E0004) (1 g) was obtained

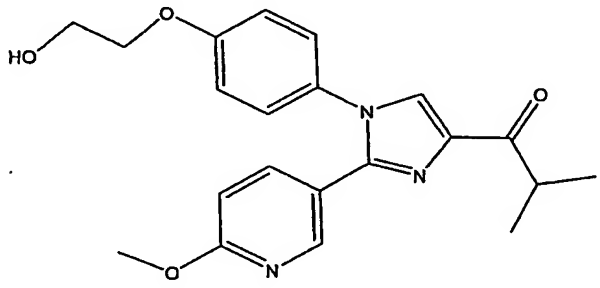
from 4-[4-difluoromethyl-2-(2-methoxypyridin-5-yl)-1H-imidazol-1-yl]phenol (1 g) and chloroacetonitrile (0.4 ml) in the similar manner that of E0001 as an oil.

NMR (DMSO-d_6) δ; 3.83 (3H, s), 5.25 (2H, s), 6.80 (1H, d, J=8.7Hz), 7.01 (1H, t, J=54.8Hz), 7.18 (2H, dd, J=7.0Hz, 1.9Hz), 7.43 (2H, dd, J=7.0Hz, 1.9Hz), 7.63 (1H, dd, J=8.7Hz, 2.2Hz), 7.86 (1H, t, J=2.1Hz), 8.07 (1H, d, J=2.2Hz).

IR (Neat): 3574, 3431, 3415, 3213, 3157, 3118, 3078, 2960, 2860, 1726, 1660, 1604 cm^{-1}.

Mass m/e : 357 (M^++1).

Example 5



(E0005)

E0005 was obtained from P0022 in a similar manner to that of E0001.

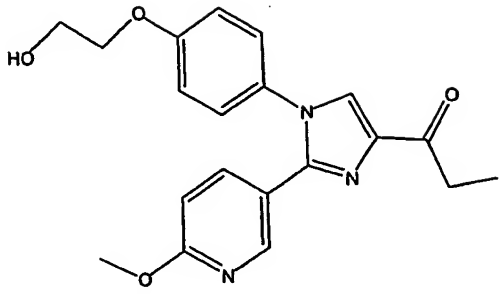
m.p. 1118.2-118.5 ℃

NMR (DMSO-d_6) δ; 1.14 (6H,d, J=6.8Hz), 3.56-3.66 (1H, m), 3.70-3.77 (2H, m), 3.83 (3H, s), 4.04 (2H, t, J=5.0 Hz), 4.91 (1H, t, J=5.4Hz), 6.82 (1H, d, J=8.7Hz), 7.05 (2H, dd, J=9.4Hz, 2.0Hz), 7.34 (2H, dd, J=9.4Hz, 2.0Hz), 7.66 (1H, dd, J=8.7Hz, 2.3Hz), 8.08 (1H, d, J=2.3Hz), 8.18 (1H, s).

IR (KBr): 3340, 3140, 3070, 2968, 2933, 1664, 1608 cm^{-1}.

Mass m/e : 382 (M^++1).

Example 6



(E0006)

E0006 was obtained from P0024 in a similar manner to that of E0001.

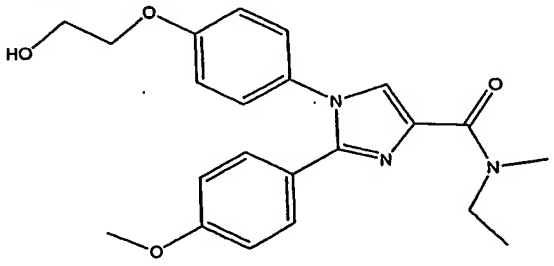
m.p. 100-104 ℃

NMR (DMSO-d_6) δ; 1.10 (3H, t, J=7.4Hz), 2.96 (2H, q, J=7.4Hz), 3.73 (2H, q, J=4.8Hz), 3.84 (3H, s), 3.98 -4.08 (2H, m), 4.91 (1H, t, J=5.4Hz), 6.81 (1H, d, J=8.6Hz), 7.04 (2H, dt, J=9.6Hz, 2.8Hz), 7.32 (2H, dt, J=9.6Hz, 2.8Hz), 7.65 (1H, dd, J=8.6 hz, 2.4Hz), 8.08 (1H, d, J=2.4Hz), 8.17 (1H, s).

IR (KBr): 3332, 3138, 2976, 2935, 1672, 1610 cm^{-1}.

Mass m/e : 368 (M^++1).

Example 7



(E0007)

E0007 was obtained in a similar manner to that of E0001.

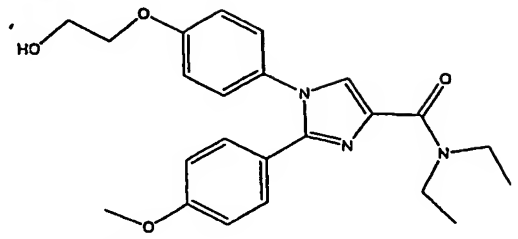
m.p. 124-126 ℃

NMR (DMSO-d_6) δ; 1.08-1.28 (3H, m), 2.90-3.02 (2H, m), 3.40-3.54 (2H, m), 3.74 (3H, s), 3.69-3.77 (1H, m), 3.98-4.00 (2H, m), 4.03 (2H, t, J=5.0Hz), 4.91 (1H, t, J=5.0Hz), 6.89 (2H, d, J=8.8Hz), 7.02 (2H, d, J=8.9Hz), 7.24-7.29 (4H, m), 7.72 (1H, s).

IR (KBr): 3367, 3126, 3072, 2968, 2933, 2875, 2839, 1604 cm^{-1}.

Mass m/e : 396 (M^++1).

Example 8



(E0008)

E0008 was obtained in a similar manner to that of E0001.

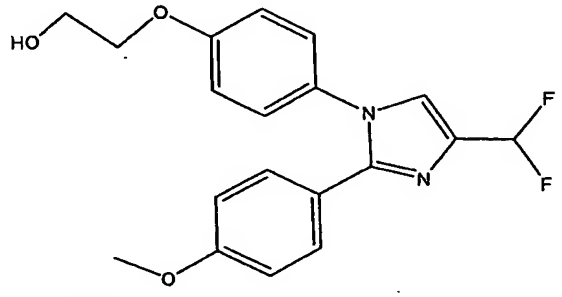
m.p. 141-143 ℃

NMR (DMSO-d_6) δ; 1.10-1.30 (6H, m), 3.28-3.50 (2H, m), 3.67-3.78 (2H, m), 3.74 (3H, s), 3.80-4.06 (2H, m), 4.03 (2H, t, J=4.9Hz), 4.91 (1H, t, J=9.2 Hz), 6.90 (2H, d, J=8.8Hz), 7.02 (2H, d, J=8.8Hz), 7.26 (4H, d, J=8.8Hz), 7.71 (1H, s).

IR (KBr): 3398, 3365, 3224, 3126, 2970, 2931, 2875, 1601 cm^{-1}.

Mass m/e : 410 (M^++1).

Example 9



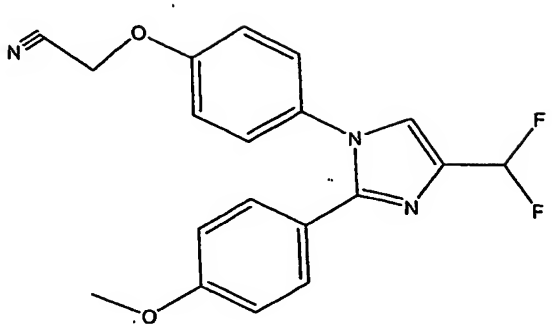
(E0009)

E0009 was obtained according to a similar manner to that of E0001.

1H NMR ($CDCl_3$, ppm) δ; 3.78 (3H, s), 3.92-4.05 (2H, m), 4.05-4.18 (2H, m), 6.77 (1H, d, J=111.66 Hz), 6.72-6.85 (2H, m), 6.89-7.00 (2H, m), 7.09-7.22 (2H, m), 7.27-7.40 (3H, m),

MS (ESI, m/e) 361 (M^++1)

Example 10



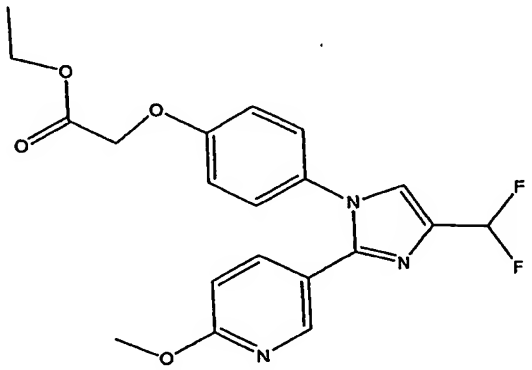
(E0010)

E0010 was obtained according to a similar manner to that of E0001.

1H NMR ($CDCl_3$, ppm) δ; 3.79(3H, s), 4.82(2H, s), 6.73-6.88(2H, m), 6.95-7.09(2H, m), 7.18-7.39(5H, m),

MS (ESI, m/e) 356(M^++1)

Example 11



(E0011)

4-Difluoromethyl-1-(4-hydroxyphenyl)-2-(2-methoxy-5-pyridyl)-1H-imidazole (300 mg) and sodium hydride (60% in oil) (42 mg) in N,N-dimethylformamide (3 ml) was stirred at room temperature for 30 minutes. Then ethyl bromoacetate (115 ml) was added and stirred at room temperature for 1 hour. Then the reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography silica-gel eluting with (n-Hexane:Ethyl acetate=2:1) to give ethyl {4-[4-(difluoromethyl)-2-(2-methoxypyridin-5-yl)-1H-imidazol-1-yl]phenoxy}acetate (E0011) (0.36 g) as an oil.

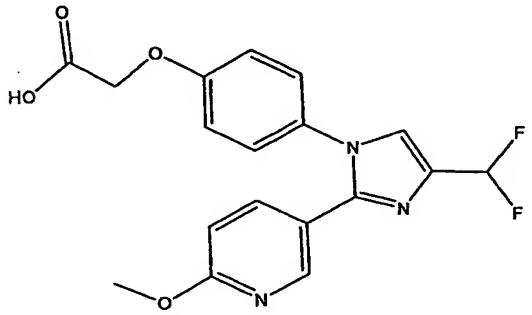
NMR (DMSO-d_6) δ; 1.21 (3H, t, J=7.1Hz), 3.83 (3H, s), 4.17 (2H, q, J=7.1Hz), 4.86 (2H, s), 6.79 (1H, d, J=8.6Hz), 7.00 (1H, t,

J=54.9Hz), 7.04 (2H, dd, J=6.9Hz, 2.2Hz), 7.33 (2H, dd, J=6.9Hz, 2.2Hz), 7.64 (1H, dd, J=8.6Hz, 2.4Hz), 7.82 (1H, t, J=2.3Hz), 8.05 (1H, d, J=2.4Hz).

IR (Neat): 3448, 3153, 3114, 3076, 2983, 2951, 1755, 1738, 1608 cm^{-1}.

Mass m/e : 404 (M^++1).

Example 12



(E0012)

1N aqueous sodium hydroxide (0.79 ml) was added to a solution of E0011 (160 mg) in ethanol (2 ml). After stirring at room temperature for 1 hour, the reaction mixture was poured into water and ethyl acetate, and extracted with water. Then the water layer was acidified with 10% aqueous potassium hydrogen sulfate, extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The resulting precipitates were collected by filtration and washed with diisopropyl ether to give E0012 (126 mg).

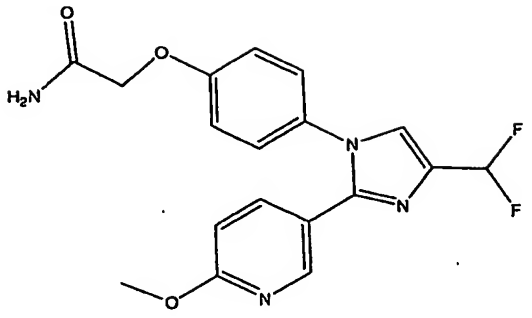
m.p. 122-124℃

NMR (DMSO-d_6) δ; 3.83 (3H, s), 4.75 (2H, s), 6.80 (1H, d, J=8.8Hz), 7.00 (1H, t, J=54.8Hz), 7.00-7.06 (2H, m), 7.32 (2H, dd, J=9.6Hz, 3.2Hz), 7.63 (1H, dd, J=8.8Hz, 2.4Hz), 7.82 (1H, t, J=2.1Hz), 8.07 (1H, d, J=2.4Hz), 13.09 (1H, br).

IR (KBr): 3465, 3446, 3122, 3066, 3010, 2966, 2522, 1738, 1651, 1612 cm^{-1}.

Mass m/e : 376 (M^++1).

Example 13



(E0013)

A mixture of E0011 (210 mg) and sodium methoxide (84 mg) in formamide (3 ml) was stirred at 100℃ for 1 hour. After cooling to room temperature, the reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The resulting precipitates were collected by filtration and washed with diisopropyl ether to give E0013 (144 mg).

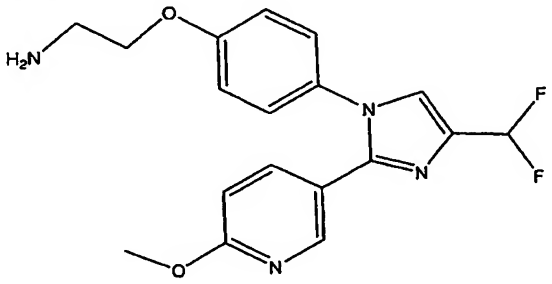
m.p. 140-141℃

NMR (DMSO-d_6) δ; 3.83 (3H, s), 4.49 (2H, s), 6.80 (1H, d, J=8.5Hz), 7.00 (1H, t, J=54.9Hz), 7.05 (2H, dd, J=6.9Hz, 2.0Hz), 7.35 (2H, dd, J=9.5Hz, 2.0Hz), 7.43 (1H, s), 7.61 (1H, s), 7.63 (1H, dd, J=8.6Hz, 2.4Hz), 7.81 (1H, t, J=2.0Hz), 8.07 (1H, d, J=2.4Hz).

IR (KBr): 3467, 3284, 3170, 3107, 2956, 1684, 1645, 1610 cm^{-1}.

Mass m/e : 375 (M^++1).

Example 14



(E0014)

Lithium aluminium hydride (13 mg) was added to a solution of E0004 (83 mg) in tetrahydrofuran (2 ml). After stirring at room temperature for 1 hour, the reaction mixture was poured into saturated aqueous ammonium chloride and extracted with ethyl

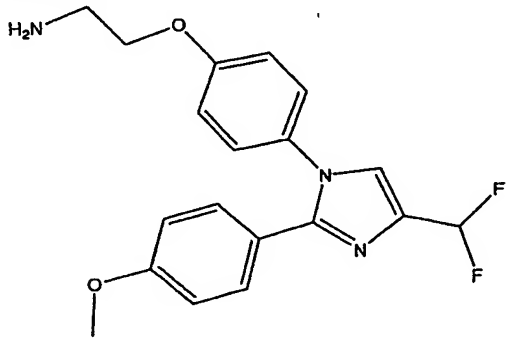
acetate, dried over magnesium sulfate and evaporated in vacuo to give E0014 (67 mg) as an oil.

NMR (DMSO-d_6) δ; 2.88 (2H, t, J=5.7Hz), 3.78 (2H, s), 3.83 (3H, s), 3.96 (2H, t, J=5.7Hz), 6.80 (1H, d, J=8.7Hz), 6.82 (1H, t, J=54.1Hz), 6.99-7.06 (2H, m), 7.28-7.34 (2H, m), 7.63 (1H, dd, J=8.7Hz, 2.4Hz), 7.80 (1H, t, J=2.0Hz), 8.07 (1H, d, J=2.4Hz).

IR (Neat): 3359, 3276, 3219, 3157, 3113, 3082, 3016, 2954, 2881, 1653, 1610 cm^{-1}.

Mass m/e : 361 (M^++1).

Example 15

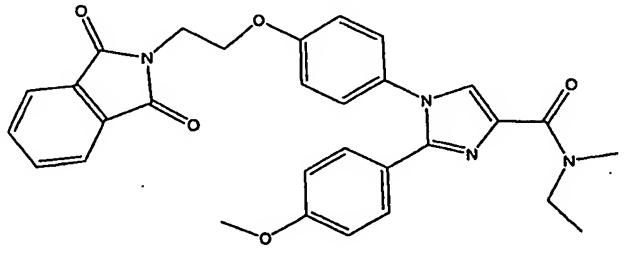


(E0015)

E0015 was obtained according to a similar manner to that of E0014.

MS (ESI, m/e) 360 (M^++1)

Example 16



(E0016)

A mixture of E0007 (0.22 g), phthalimide (128 mg), triphenylphosphine (219 mg) and diethylazocarboxylate (131 ml) in tetrahydrofuran (2 ml) was stirred at room temperature for 2 hours. The reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography

silica-gel eluting with (n-Hexane:Ethyl acetate=1:1 - 0:1). The resulting precipitates were collected by filtration and washed with diisopropyl ether to give E0016 (235 mg).

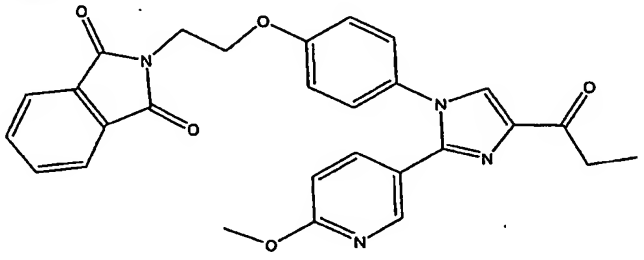
m.p. 135-136℃

NMR (DMSO-d_6) δ; 1.08-1.28 (3H, m), 2.89-3.02 (2H, m), 3.40-3.50 (2H, m), 3.73 (3H, s), 3.69-3.77 (1H, m), 3.99 (2H, t, J=5.4 Hz), 4.27 (2H, t, J=5.4Hz), 6.87 (2H, d, J=8.8Hz), 6.98 (2H, d, J=8.9Hz), 7.24 (4H, d, J=8.8Hz), 7.68 (1H, s), 7.83-7.93(4H, m).

IR (KBr): 3537, 3431, 3305, 3236, 3143, 2970, 2935, 1716, 1649, 1610 cm^{-1}.

Mass m/e : 525 (M^++1).

Example 17



(E0017)

E0017 was obtained in a similar manner to that of E0016.

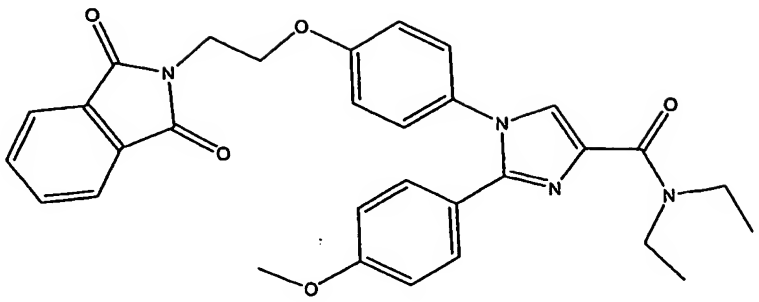
m.p. 155-157 ℃

NMR (DMSO-d_6) δ; 1.09 (3H, t, J=7.3Hz), 2.95 (2H, q, J=7.3Hz), 3.83 (3H, s), 3.98 (2H, t, J=5.7Hz), 4.27 (2H, t, J=5.7Hz), 6.79 (1H, d, J=8.6Hz), 7.00 (2H, d, J=8.9Hz), 7.30 (2H, d, J=8.8Hz), 7.61 (1H, dd, J=8.6Hz, 2.5Hz), 7.83-7.93 (4H, m), 7.93 (1H, d, J=2.5Hz), 8.13 (1H, s).

IR (KBr): 3207, 3140, 3066, 2970, 2941, 1712, 1674, 1610 cm^{-1}.

Mass m/e : 497 (M^++1).

Example 18



(E0018)

E0018 was obtained in a similar manner to that of E0016.

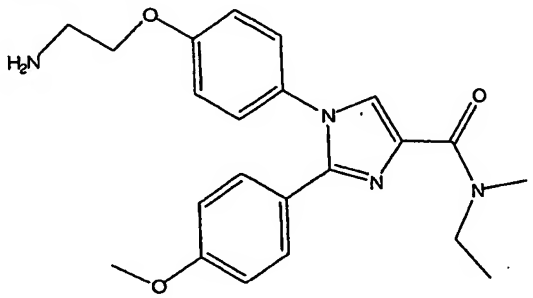
m.p. 109-111 ℃

NMR (DMSO-d_6) δ; 1.08-1.30 (6H, m), 3.32-3.51 (2H, m), 3.72 (3H, s), 3.80-3.96 (2H, m), 3.99 (2H, t, J=5.9Hz), 4.27 (2H, t, J=5.9 Hz), 6.87 (2H, d, J=8.9Hz), 6.98 (2H, d, J=8.9Hz), 7.24 (4H, d, J=8.8Hz), 7.67 (1H, s), 7.83-7.91 (4H, m).

IR (KBr): 3419, 3215, 3143, 3053, 2970, 2935, 2879, 2841, 1776, 1712, 1608 cm^{-1}.

Mass m/e : 539 (M^++1).

Example 19



(E0019)

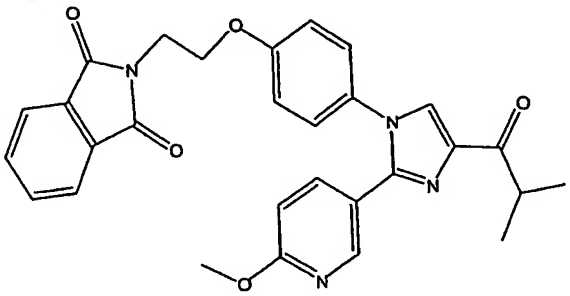
E0016 (220 mg) and hydrazine hydride (203 ml) in acetonitrile (3 ml) was stirred at reflux condition for 2 hours. After cooling at room temperature, The reaction mixture was poured into 1N aqueous sodium hydroxide and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The resulting precipitates were corrected by filtration and washed with diisopropyl ether to give E0019 (157 mg).

m.p. 134-135℃

NMR (DMSO-d_6) δ; 1.09-1.30 (3H, m), 1.78 (2H, br), 2.88 (2H. t,

J=5.7Hz), 2.89-3.00 (2H, m), 3.40-3.53 (2H, m), 3.74 (3H, s), 3.69-3.77 (1H, m), 3.94 (2H, t, J=5.7 Hz), 6.89 (2H, d, J=8.8Hz), 7.01 (2H, d, J=8.9Hz), 7.26 (4H, d, J=8.8Hz), 7.72 (1H, s).
IR (KBr): 3427, 3377, 3350, 3209, 3105, 3066, 2962, 2935, 2877, 2835, 1606 cm^{-1}.
Mass m/e : 395 (M^++1).

Example 20



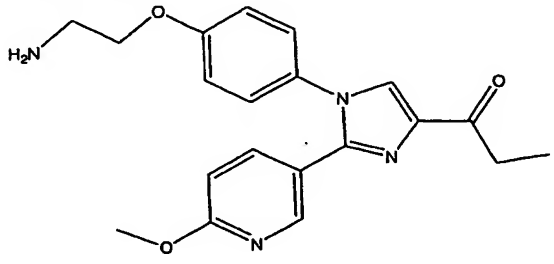
(E0020)

E0020 was obtained in a similar manner to that of E0016.

m.p. 118-120 ℃

NMR (DMSO-d_6) δ; 1.14 (6H,d, J=6.8Hz), 3.56-3.67(1H, m), 3.83 (3H, s), 3.96-4.09 (4H, m), 6.79 (1H, d, J=8.6Hz), 7.00 (2H, d, J=8.9Hz), 7.31 (2H, d, J=8.9Hz), 7.61 (1H, dd, J=8.6Hz, 2.4Hz), 7.85-7.91 (4H, m), 8.08 (1H, d, J=2.4Hz), 8.98 (1H, s).
IR (KBr): 3246, 3141, 3041, 2983, 2935, 2875, 1749, 1707, 1670, 1610 cm^{-1}.
Mass m/e : 511 (M^++1).

Example 21



(E0021)

E0021 was obtained in a similar manner to that of E0019.

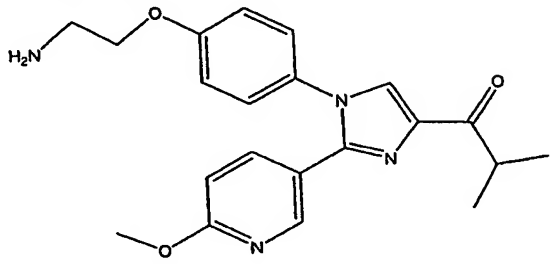
m.p. 112-113 ℃

NMR (DMSO-d_6) δ; 1.10 (3H, t, J=7.4Hz), 1.59 (2H, br), 2.88 (2H, t, J=5.7Hz), 2.96 (2H, q, J=7.4Hz), 3.84 (3H, s), 3.96 (2H, t, J=5.7Hz), 6.82 (1H, d, J=8.6Hz), 7.02-7.08 (2H, m), 7.28-7.36 (2H, m), 7.66 (1H, dd, J=8.6Hz, 2.4Hz), 8.08 (1H, d, J=2.4Hz), 8.17 (1H, s).

IR (KBr): 3359, 3296, 3138, 3055, 2947, 1670, 1608 cm^{-1}.

Mass m/e : 367 (M^++1).

Example 22



(E0022)

E0022 was obtained in a similar manner to that of E0019.

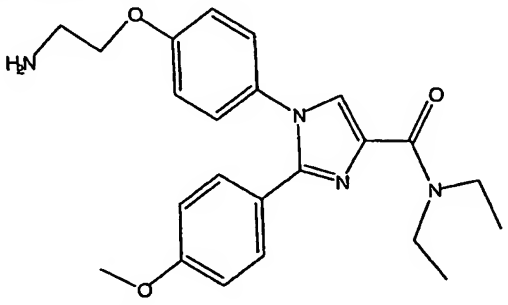
m.p. 93-94 ℃

NMR (DMSO-d_6) δ; 1.14 (6H,d, J=6.8Hz), 3.31-3.40 (2H, m), 3.59-3.66 (1H, m), 3.84 (3H, s), 4.00 (2H, t, J=5.4Hz), 5.53 (2H, s), 6.18 (1H, t, J=5.4Hz), 6.82 (1H, d, J=8.7Hz), 7.05(2H, d, J=8.9Hz), 7.34 (2H, d, J=8.9Hz), 8.65 (1H, dd, J=8.7Hz, 2.3Hz), 8.09 (1H, d, J=2.3Hz), 8.18(1H, s).

IR (KBr): 3375, 3311, 3217, 3091, 2966, 2937, 2871, 1658, 1608 cm^{-1}.

Mass m/e : 381 (M^++1).

Example 23



(E0023)

E0023 was obtained in a similar manner to that of E0019.

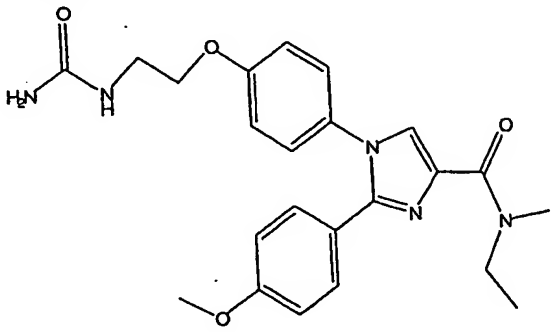
m.p. 108-109 ℃

NMR (DMSO-d_6) δ; 1.03-1.30 (6H, m), 1.46-1.76 (2H, br), 2.88 (2H, t, J=5.7Hz), 3.17-3.50 (2H, m), 3.74 (3H, s), 3.80-4.07 (2H, m), 3.95 (2H, t, J=5.7Hz), 6.89 (2H, d, J=8.8Hz), 7.02 (2H, d, J=8.8Hz), 7.26 (4H, d, J=8.8Hz), 7.71 (1H, s).

IR (KBr): 3458, 3425, 3390, 3365, 2972, 2933, 2887, 1604 cm^{-1}.

Mass m/e : 409 (M^++1).

Example 24



(E0024)

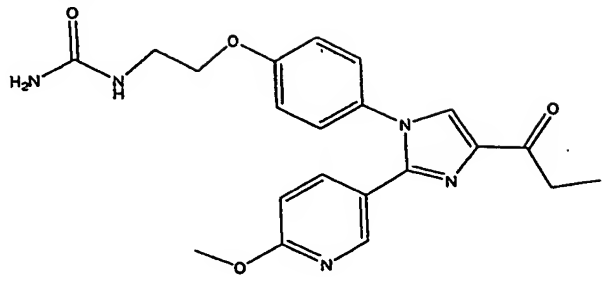
Triethylamine (16 ml) and trimethylsilyl isocyanate (74 ml) was added to a solution of E0019 (80 mg) in dichloromethane (2 ml) under stirring at 0℃. After stirring at 0℃ for 1 hour, the reaction mixture was poured into 1N aqueous hydrogen chloride and stirred at room temperature for 5 minutes. Then the mixture was alkalinized with saturated sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The resulting precipitates were corrected by filtration and washed with diisopropyl ether to give E0024 (6 mg).

NMR (DMSO-d_6) δ; 1.10-1.28 (5H, m), 2.89-3.00 (2H, m), 3.40-3.53 (2H, m), 3.74 (3H, s), 3.98-4.08(1H, m), 3.98 (2H, t, J=5.7 Hz), 5.54 (2H, s), 6.55 (1H, s), 6.89 (2H, d, J=8.8Hz), 7.03 (2H, d, J=8.9Hz), 7.26 (4H, d, J=8.8Hz), 7.72 (1H, s).

IR (KBr): 3431, 3359, 3290, 3275, 3240, 2960, 2925, 2856, 1734, 1697, 1649, 1614 cm^{-1}.

Mass m/e : 438 (M^++1).

Example 25



(E0025)

E0025 was obtained in a similar manner to that of E0024.

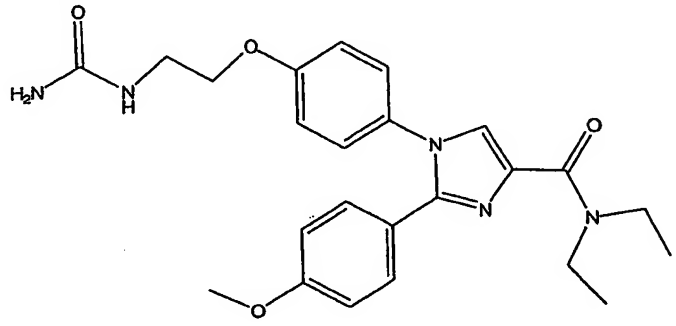
m.p. 109-111 ℃

NMR (DMSO-d_6) δ; 1.10 (3H, t, J=7.3Hz), 2.95 (2H, q, J=7.3Hz), 3.84 (3H, s), 3.99 (2H, t, J=5.5Hz), 5.54 (2H, s), 6.18 (1H, t, J=5.6Hz), 6.81 (1H, d, J=8.6Hz), 7.05 (2H, d, J=8.9Hz), 7.33 (2H, d, J=8.8Hz), 7.65 (1H, dd, J=8.6Hz, 2.3Hz), 8.09 (1H, d, J=2.3Hz), 8.17 (1H, s), 11.09 (2H, br).

IR (KBr): 3444, 3217, 3039, 2885, 2831, 2783, 1772, 1722, 1610 cm^{-1}.

Mass m/e : 410 (M^++1).

Example 26



(E0026)

E0026 was obtained in a similar manner to that of E0024.

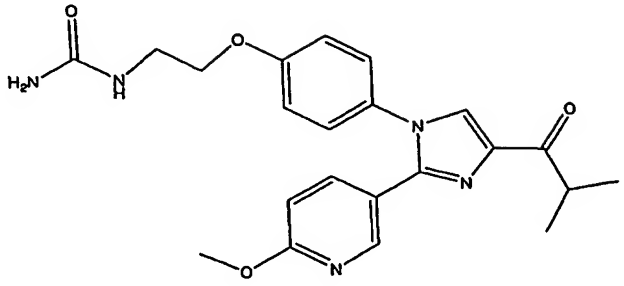
m.p. 167-169 ℃

NMR (DMSO-d_6) δ; 1.10-1.30 (6H, m), 3.28-3.56 (4H, m), 3.74 (3H, s), 3.82-3.98 (2H, m), 3.97 (2H, t, J=5.4Hz), 5.54 (2H, s), 6.18 (1H, t, J=5.4Hz), 6.89 (2H, d, J=8.9Hz), 7.03 (2H, d, J=8.9Hz), 7.26 (4H, d, J=8.8Hz), 7.71 (1H, s).

IR (KBr): 3406, 3359, 3232, 2970, 2935, 2879, 2837, 1680 cm^{-1}.

Mass m/e : 452 (M^++1).

Example 27



(E0027)

E0027 was obtained in a similar manner to that of E0024.

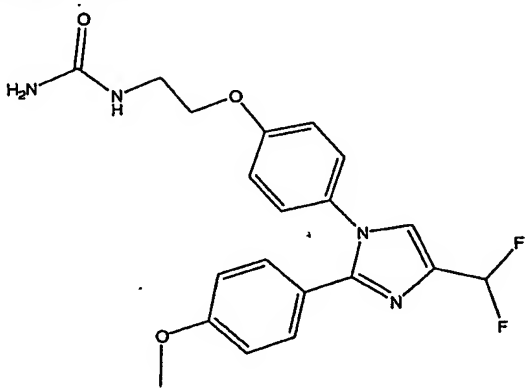
m.p. 170-172 ℃

NMR (DMSO-d_6) δ; 1.14 (6H,d, J=6.9Hz), 3.33-3.43 (2H, m), 3.57-3.60 (1H, m), 3.84 (3H, s), 4.00 (2H, t, J=5.6Hz), 5.54 (2H, s), 6.18 (1H, t, J=5.6Hz), 6.82 (1H, d, J=8.7Hz), 7.05 (2H, d, J=8.9Hz), 7.34 (2H, d, J=8.9Hz), 7.65 (1H, dd, J=8.7Hz, 2.3Hz), 8.09 (1H, d, J=2.3Hz), 8.18 (1H, s).

IR (KBr): 3473, 3390, 3338, 3089, 3026, 2969, 2877, 1662, 1606 cm^{-1}.

Mass m/e : 424 (M^++1).

Example 28

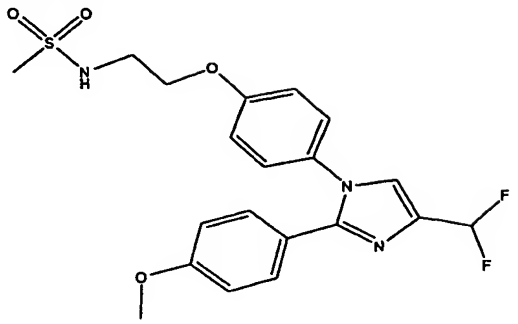


(E0028)

E0028 was obtained according to a similar manner to that of E0024.

MS (ESI, m/e) 403(M^++1)

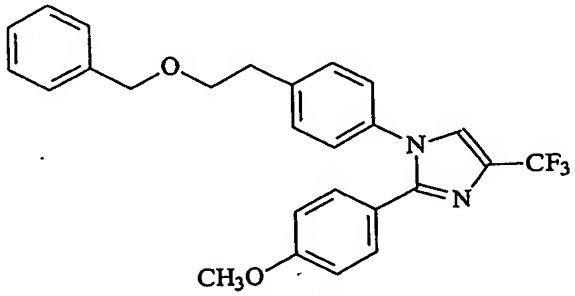
Example 29



(E0029)

To a solution of E0015 and triethylamine (87 μl) in dichloromethane (2 ml) was added methane methylsulofonyl chloride (48 μl) at room temperature. After stirring for 2 hours, the reaction mixture was poured into water and dichloromethane. The aqueous layer was separated and extracted with dichloromethane. The combined layer was washed with water and brine, dried over magnesium sulfate, filtered and evaporated under reduces pressure. The residue was column chromatographed on silica gel (10 g) and crystallized to give E0029 (128 mg).
NMR ($CDCl_3$) δ; 3.04 (3H, s), 3.57 (2H, q, J=5.3Hz), 3.78 (3H, s), 4.06-4.20 (2H, m), 4.90 (1H, bt, J=6.0Hz), 6.77 (1H, bt, J=55 Hz), 6.70-6.85(2H, m), 6.86-6.98(2H, m), 7.10-7.20(2H, m), 7.29-7.38(3H, m),
MS (ESI, m/e) 438(M^++1)

Example 30



(E0030)

A mixture of N^1-(4-(2-benzyloxy)ethylphenyl)-4-methoxy-benzamidine (0.5 g), 3-bromo-1,1,1-trifluoropropan-2-one

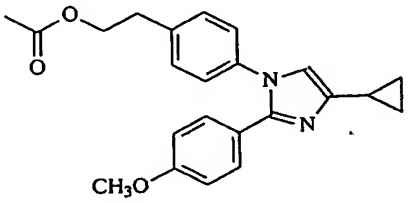
(0.216 ml) and sodium hydrogencarbonate (233 mg) in isopropyl alcohol (5 ml) was stirred at reflux condition for overnight. After cooling to room temperature, the reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was dissolved in acetic acid (5 ml) and refluxed for 1 hour. After cooling to room temperature, the reaction mixture was poured into aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography silica gel eluting with (n-Hexane : Ethyl acetate= 1:1) to give E0030 (0.33 g).

NMR (DMSO-d_6) δ; 2.927 (2H, t, J=6.2Hz), 3.681 (2H, t, J=6.5Hz), 3.724 (3H, s), 4.486 (2H, s), 6.855 (2H, d, J=8.5Hz), 7.237-7.355 (9H, m), 7.377 (2H, d, J=8.5Hz), 8.125 (1H, d, J=1Hz)

IR (Neat): 2960, 2858, 1738, 1697, 1687, 1649, 1612 cm^{-1}

Mass (ESI^+, m/e): 453 (M^++1)

Example 31



(E0031)

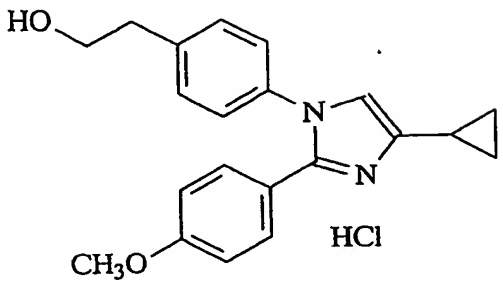
E0031 was obtained in the similar manner to that of E0030.

NMR (DMSO-d_6) δ; 0.71-0.84 (4H, m), 1.62 (3H, s), 2.06-2.19 (1H, m), 2.927 (2H, t, J=6.5Hz), 3.72 (3H, s), 4.233 (2H, t, J=6.7Hz), 6.8-6.85 (2H, m), 7.13-7.23 (5H, m), 7.29-7.35 (2H, m)

IR (Neat): 3430, 3405, 3257, 3089, 3006, 2960, 2929, 2858, 1728, 1664, 1608 cm^{-1}

Mass (ESI^+, m/e): 377 (M^++1)

Example 32



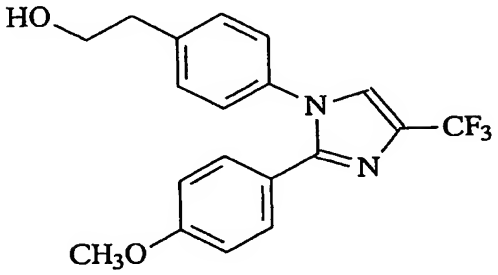
(E0032)

To a solution of E0031 (200 mg) was added 1N aqueous sodium hydroxide (1.06 ml) in methanol (2 ml). After stirring at room temperature for 1 hour, the reaction mixture was poured into water and ethyl acetate, and extracted with water. Then the water layer was acidified with 1N aqueous hydrochloride, extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was dissolved in ethyl acetate (1 ml) and 4N hydrogen chloride/ethyl acetate (97 µl) was added. Resulting precipitates were collected by filtration and washed with diisopropyl ether to give E0032 (52 mg).

NMR (DMSO-d_6) δ; 0.89-0.93 (2H, m), 1.03-1.08 (2H, m), 2.01-2.08 (1H, m), 2.778 (2H, t, J=3.3Hz), 3.624 (2H, t, J=3.3Hz), 3.786 (3H, s), 7.02 (2H, d, J=4.4Hz), 7.323-7.386 (6H, m), 7.691 (1H, s)

IR (KBr): 3383, 3311, 3080, 2945, 1697, 1685, 1637, 1614 cm^{-1}

Example 33



(E0033)

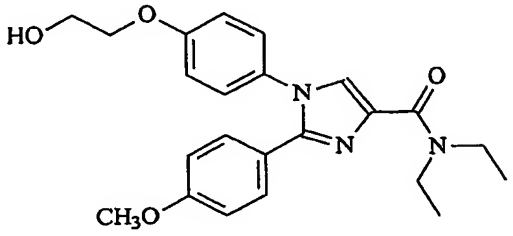
E0030 (0.33 g) and dry 20% $Pd(OH)_2/C$ (100 mg) in ethanol (6 ml) and cyclohexene (3 ml) was stirred at reflux condition for 4 hours and cooled to room temperature. After filtration, the reaction mixture was evaporated in vacuo to give E0033 (0.19

g).

NMR (DMSO-d_6) δ; 3.728 (2H, t, J=7.3Hz), 3.742 (3H, s), 4.026 (2H, t, J=4.7Hz), 4.911 (1H, t, J=5Hz), 6.892 (2H, d, J=9Hz), 7.03 (2H, d, J=9Hz), 7.253-7.331 (4H, m), 8.068 (1H, d, J=1Hz)

Mass (ESI^+, m/e): 363 (M^++1)

Example 34



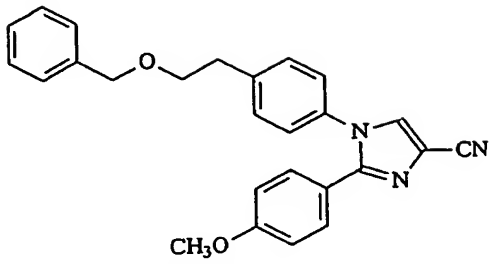
(E0034)

4-(N,N-Diethylcarbamoyl)-1-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole (400 mg), 2-chloroethanol (0.44 ml), potassium carbonate (908 mg) and potassium iodide (1.09 mg) in N,N-dimethylformamide (2 ml) was stirred at 75 ℃ for 6 hours. Then the reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography silica-gel eluting with (n-Hexane:Ethyl acetate=1:1) to give E0034 (0.37 g).

NMR (DMSO-d_6) δ; 1.072-1.273 (6H, m), 3.324-3.482 (2H, m), 3.691-3.781 (2H, m), 3.735 (3H, s), 3.841-3.981 (2H, m), 4.025 (2H, t, J=4.7Hz), 4.907 (1H, t, J=5Hz), 6.888 (2H, d, J=9Hz), 7.022 (2H, d, J=8.5Hz), 7.241-7.284 (4H, m), 7.71 (1H, s)

Mass (ESI^+, m/e): 410 (M^++1)

Example 35



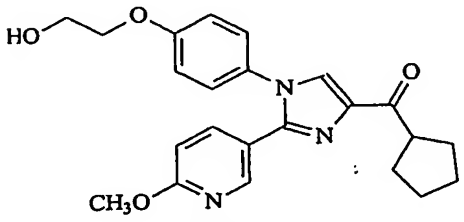
(E0035)

A mixture of P0037 (1.2 g) and manganese(IV) oxide (1.27 g) in N,N-dimethylformamide (15 ml) was stirred at 100℃ for 6 hours. After filtration, the reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. To the solution of the residue in N,N-dimethylformamide (10 ml) phosphorus oxychloride (0.27 ml) was added under stirring at 0℃. After stirring at room temperature for 1 hour, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo to give E0035 (1.0 g).

NMR (DMSO-d_6) δ; 2.926 (2H, t, J=3.2Hz), 3.677 (2H, t, J=3.2Hz), 3.723 (3H, s), 4.48 (2H, s), 6.861 (2H, d, J=4.5Hz), 7.243-7.322 (9H, m), 7.381 (2H, d, J=4.2Hz), 8.447 (1H, s)

Mass (ESI^+, m/e): 410 (M^++1)

Example 36



(E0036)

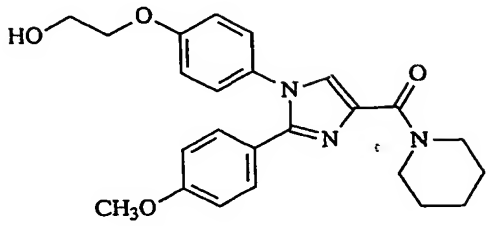
E0036 was obtained in the similar manner to that of E0034.

NMR (DMSO-d_6) δ; 1.573-1.988 (8H, m), 3.697-3.85 (3H, m), 3.837 (3H, s), 4.036 (2H, t, J=4.7Hz), 4.914 (1H, t, J=5.3Hz), 6.815 (1H, d, J=9.5Hz), 7.042 (2H, d, J=9Hz), 7.333 (2H, d, J=9Hz), 7.662 (1H, dd, J=2.5Hz, 8.5Hz), 8.079 (1H, d, J=1.5Hz), 8.183

(1H, s)

Mass (ESI$^+$, m/e): 408 (M^++1)

Example 37



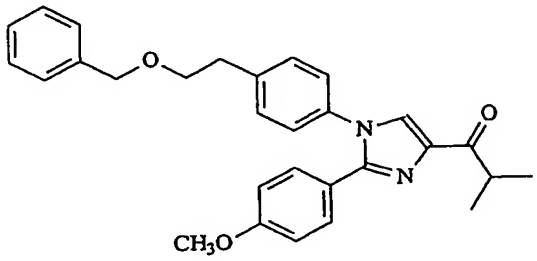
(E0037)

E0037 was obtained in the similar manner to that of E0034.

NMR (DMSO-d_6) δ; 1.475-1.726 (6H, m), 3.484-4.251 (6H, m), 3.734 (3H, s), 4.021 (2H, t, J=4.7Hz), 4.906 (1H, t, J=5Hz), 6.884 (2H, d, J=9Hz), 7.013 (2H, d, J=8.5Hz), 7.233-7.283 (4H, m), 7.712 (1H, s)

Mass (ESI$^+$, m/e): 422 (M^++1)

Example 38



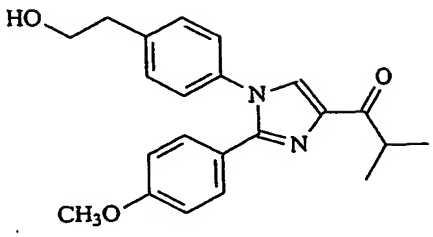
(E0038)

E0038 was obtained in the similar manner to that of Preparation 23.

NMR (DMSO-d_6) δ; 1.136 (6H, d, J=7Hz), 2.924 (2H, t, J=6.5Hz), 3.592-3.722 (3H, m), 3.724 (3H, s), 4.487 (2H, s), 6.859 (2H, d, J=9Hz), 7.243-7.316 (9H, m), 7.321-7.366 (2H, m), 8.156 (1H, s)

Mass (ESI$^+$, m/e): 455 (M^++1)

Example 39



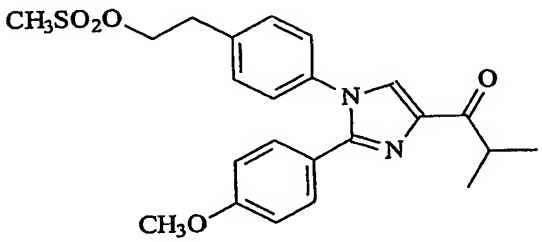
(E0039)

E0039 was obtained in the similar manner to that of E0033.

NMR (DMSO-d_6) δ; 1.137 (6H, d, J=3.4Hz), 2.779 (2H, t, J=3.3Hz), 3.595-3.657 (3H, m), 3.745 (3H, s), 4.7 (1H, t, J=2.4Hz), 6.888 (2H, d, J=4.4Hz), 7.248-7.282 (4H, m), 7.33 (2H, d, J=4.2Hz), 8.137 (1H, s)

Mass (ESI^+, m/e): 365 (M^++1)

Example 40



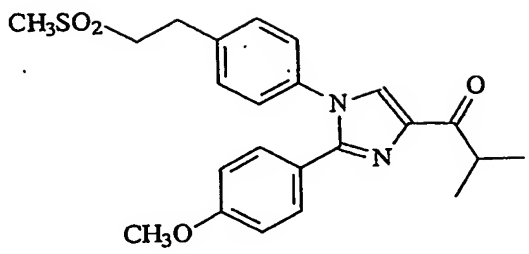
(E0040)

To a solution of E0039 (0.18 g) in dichloromethane (2 ml) was added methanesulfonyl chloride (77 μl) and triethylamine (138 μl) at 0℃. After stirring for 40 minutes at 0℃, the mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated under reduced pressure to give E0040 (0.22 g).

NMR (DMSO-d_6) δ; 1.151 (6H, d, J=7Hz), 3.067 (2H, t, J=6.5Hz), 3.11 (3H, s), 3.566-3.634 (1H, m), 3.75 (3H, s), 4.454 (2H, t, J=6.5Hz), 6.902 (2H, d, J=9Hz), 7.258-7.454 (6H, m), 8.332 (1H, s)

Mass (ESI^+, m/e): 443 (M^++1)

Example 41



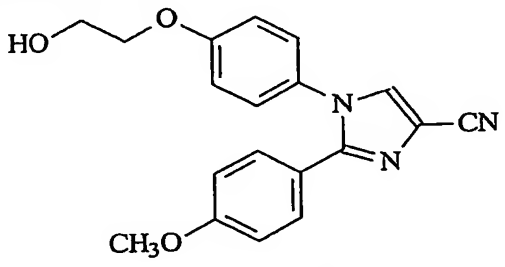
(E0041)

A solution of E0040 (0.22 g) and sodium thiomethoxide (128 g) in N,N-dimethylformamide (2 ml) was stirred at 60℃ for 4 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was dissolved in tetrehydrofura (2 ml) and OXONE (Trademark, purchased from ALDRICH) (917 mg) in water (2 ml) was added. After stirring at room temperature for 2 hours, the reaction mixture was poured into aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography silica-gel eluting with (n-Hexane:Etyl acetate=1:1) to give E0041 (110 mg).

NMR (DMSO-d_6) δ; 1.14 (6H, d, J=3.3Hz), 2.986 (3H, s), 3.061-3.102 (2H, m), 3.459-3.5 (2H, m), 3.597-3.666 (1H, m), 3.747 (3H, s), 6.885 (2H, d, J=4.5Hz), 7.262 (2H, d, J=4.4Hz), 7.316 (2H, d, J=4.2Hz), 7.426 (2H, d, J=4.2Hz), 8.161 (1H, s)

Mass (ESI^+, m/e): 427 (M^++1)

Example 42



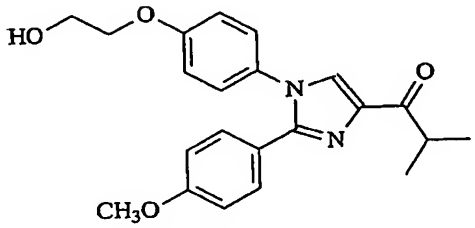
(E0042)

E0042 was obtained in the similar manner to that of E0034.

NMR ($CDCl_3$) δ; 3.79 (3H, s), 3.96-4.08 (2H, m), 4.08-4.18 (2H, m), 6.75-6.87 (2H, m), 6.91-7.02 (2H, m), 7.08-7.20 (2H, m), 7.23-7.37 (2H, m), 7.59 (1H, s)

Mass (ESI^+, m/e): 336 (M^++1)

Example 43



(E0043)

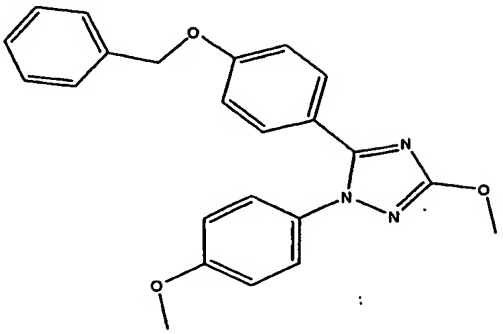
E0043 was obtained in the similar manner to that of Preparation 23.

NMR ($CDCl_3$) δ; 1.24 (3H, s), 1.28 (3H, s), 3.67-3.88 (4H, m), 3.92-4.07 (2H, m), 4.07-4.18 (2H, m), 6.75-6.87 (2H, m), 6.89-6.99 (2H, m), 7.09-7.20 (2H, m), 7.30-7.38 (2H, m), 7.74 (1H, s)

Mass (ESI^+, m/e): 381 (M^++1)

(continued to the next page)

Preparation 38



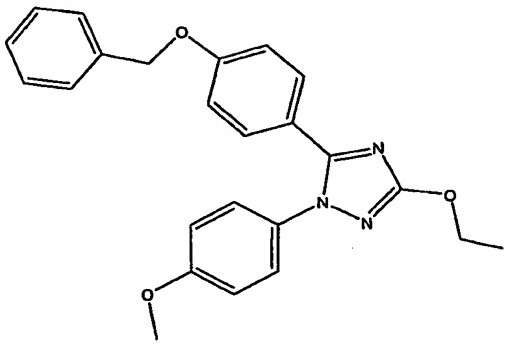
(P0038)

A mixture of P0051 (2 g, 5.36 mmol), potassium carbonate (2.22 g, 16.1 mmol) and dimethyl sulfate (0.711 ml, 7.5 mmol) in dimethylformamide (15 ml) was stirred at roomtemperature for 1.5 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated to give crude solid. The solid was purified with column chromatography (SiO2 50 g, eluted with toluene:ethyl acetate =4:1). The desired P0038 was washed with isopropylether, isolated by filtartion, and dried in vacuo (1.02 g, 49.2% yield).

1H NMR (CDCl3, ppm) d 3.84(3H, s), 4.04(3H, s), 5.05(2H, s), 6.82-7.00(4H, m), 7.27-7.55(9H, m),

MS (ESI, m/e) 388(M+1)

Preparation 39

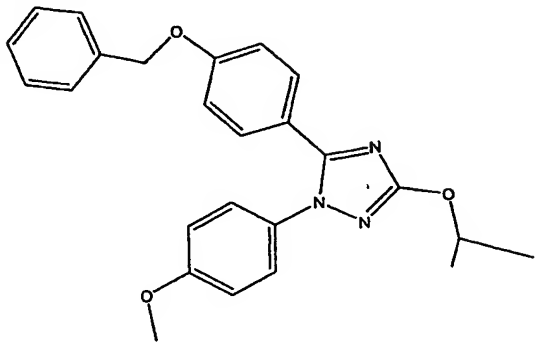


(P0039)

P0039 was obtained according to a similar manner to that of P0038.

1H NMR (CDCl3, ppm) d 1.45(3H, t, J=7.0 Hz), 3.84(3H, s), 4.39(2H, q, J=7.0 Hz), 5.05(2H, s), 6.82-6.98(4H, m), 7.20-7.50(9H, m), MS (ESI, m/e) 402(M+1)

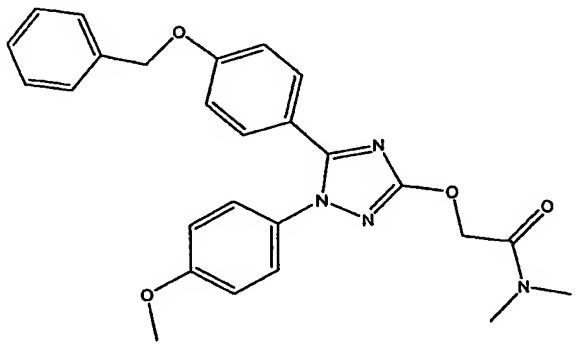
Preparation 40



(P0040)

A mixture of P0051 (1 g, 2.68 mmol), potassium carbonate (1.11 g, 8.03 mmol) and isopropyl iodide (1.34 ml, 13.4 mmol) in dimethylformamide (5 ml) was stirred at 100°C for 2 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated to give crude solid. The solid was purified with column chromatography (SiO2 50 g, eluted with toluene:ethyl acetate =5:1) (1.02 g, 49.2% yield).
1H NMR (CDCl3, ppm) d 1.43(6H, d, J=6.2 Hz), 3.84(3H, s), 4.92-5.12(4H, m), 6.81-7.00(4H, m), 7.20-7.52(9H, m), MS (ESI, m/e) 416(M+1)

Preparation 41



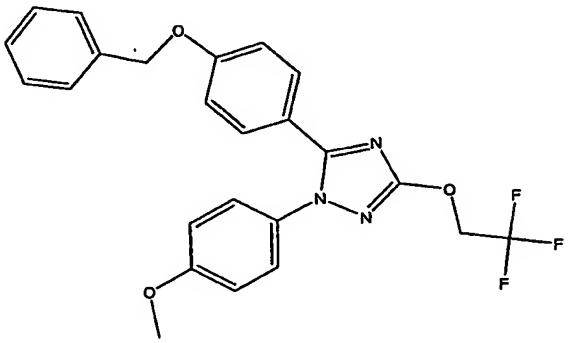
(P0041)

P0041 was obtained according to a similar manner to that of P0040.

1H NMR (DMSO-d6, ppm) d 2.84(3H, s), 2.91(3H, s), 3.80(3H, s), 5.00(2H, s), 5.10(2H, s), 7.02(4H, d, J=8.9 Hz), 7.21-7.50(9H, m),

MS (ESI, m/e) 459(M+1)

Preparation 42



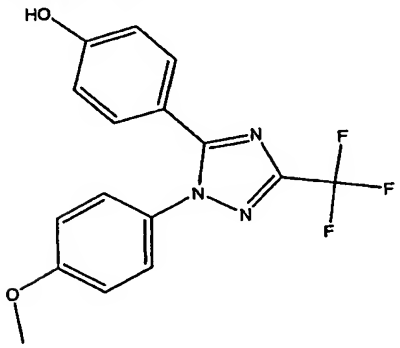
(P0042)

P0042 was obtained according to a similar manner to that of P0040.

1H NMR (CDCl3, ppm) d 3.85(3H, s), 4.74(2H, q, J=8.3 Hz), 5.06(2H, s), 6.85-7.00(4H, m), 7.21-7.54(9H, m),

MS (ESI, m/e) 456(M+1)

Preparation 43

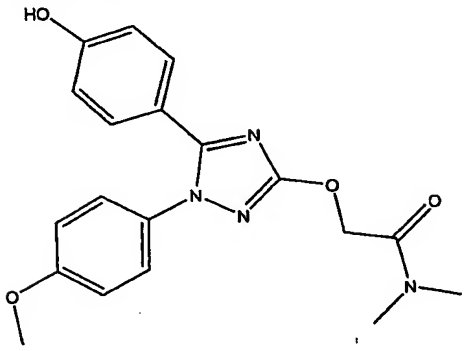


(P0043)

10% Pd/C(50% wet, 423 mg) and P0053(1.9 g, 4.47 mmol) in 20 ml of methanol were stirred under a hydrogen gas atmosphere at room temperature for 1.5 hours. After filtration, the reaction mixture

was evaporated in vacuo to give P0043 (1.39 g, 92.8% yield).
1H NMR (DMSO-d6, ppm) d 3.83(3H, s), 6.70-6.85(2H, m), 7.03-7.18(2H, m), 7.25-7.39(2H, m), 7.40-7.55(2H, m), 10.12(1H, bs),
MS (ESI, m/e) 358(M+Na)

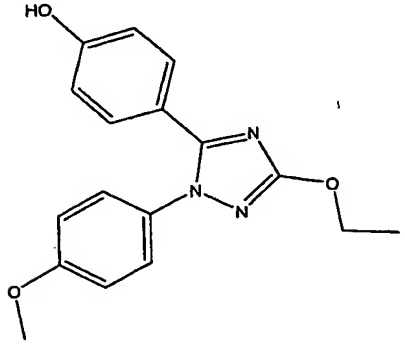
Preparation 44



(P0044)

P0044 was obtained according to a similar manner to that of P0043.
1H NMR (DMSO-d6, ppm) d 2.84(3H, s), 2.96(3H, s), 3.80(3H, s), 4.99(2H, s), 6.74(2H, d, J=8.7 Hz), 7.02(2H, d, J=8.9 Hz), 7.17-7.38(4H, m), 9.97(1H, bs),
MS (ESI, m/e) 369(M+1)

Preparation 45

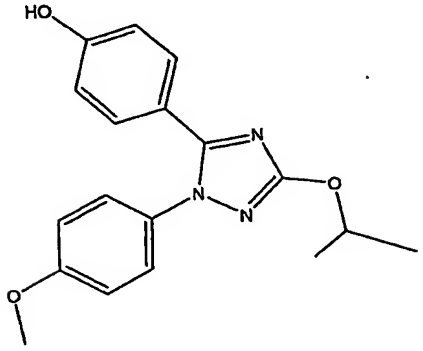


(P0045)

P0045 was obtained according to a similar manner to that of P0043.
1H NMR (DMSO-d6, ppm) d 1.35(3H, t, J=7.0 Hz), 3.80(3H, s), 4.28(2H, q, J=7.0 Hz), 6.64-6.79(2H, m), 6.95-7.08(2H, m), 7.16-7.34(4H,

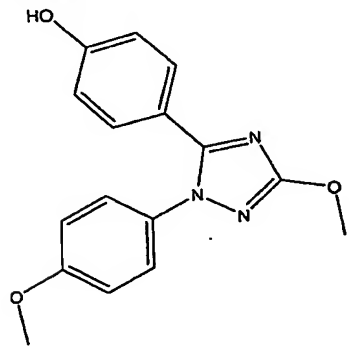
m), 9.95(1H, bs),
MS (ESI, m/e) 312(M+1)

Preparation 46



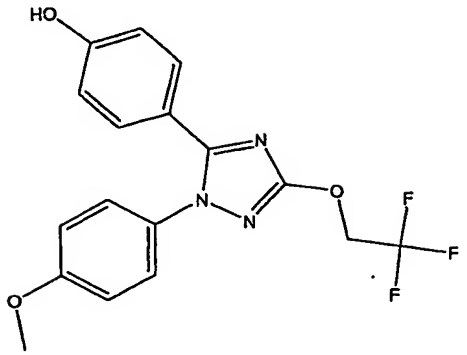
(P0046)
P0046 was obtained according to a similar manner to that of P0043.
1H NMR (CDCl3, ppm) d 1.42(6H, d, J=6.3 Hz), 3.84(3H, s), 5.01(1H, 7th, J=6.1Hz), 6.62-6.80(3H, m), 6.84-6.98(2H, m), 7.18-7.35(4H, m),
MS (ESI, m/e) 326(M+1)

Preparation 47



(P0047)
P0047 was obtained according to a similar manner to that of P0043.
1H NMR (CDCl3, ppm) d 3.84(3H, s), 4.03(3H, s), 6.59-6.74(2H, m), 6.83-6.98(2H, m), 7.16-7.35(4H, m), 8.79(1H, bs),
MS (ESI, m/e) 298(M+1)

Preparation 48



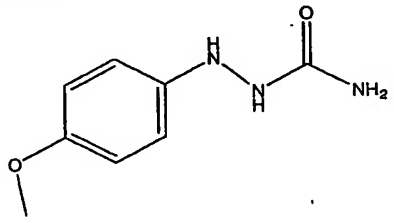
(P0048)

P0048 was obtained according to a similar manner to that of P0043.

1H NMR (DMSO-d6, ppm) d 3.81(3H, s), 4.98(2H, q, J=8.8 Hz), 6.70-6.83(2H, m), 6.98-7.10(2H, m), 7.18-7.39(4H, m),

MS (ESI, m/e) 366(M+1)

Preparation 49



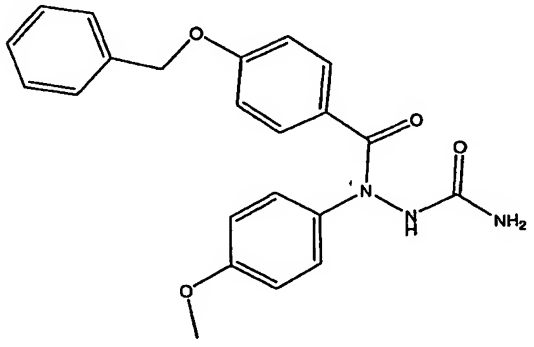
(P0049)

P0049 was obtained according to a similar manner to that of P0063.

1H NMR (DMSO-d6, ppm) d 3.65(3H, s), 5.91(2H, bs), 6.59-6.72(2H, m), 6.72-6.85(2H, m), 7.26(1H, bs), 7.65(1H, bs),

MS (ESI, m/e) 204(M+Na)

Preparation 50

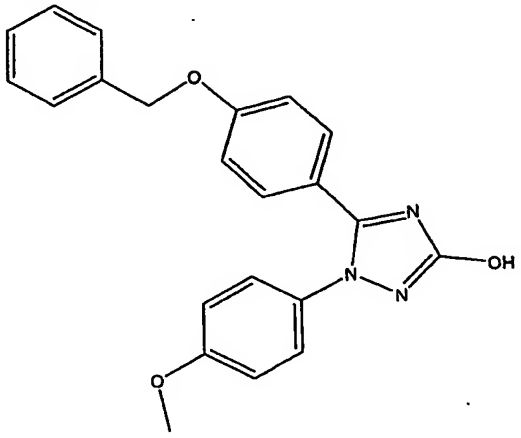


(P0050)

P0050 was obtained according to a similar manner to that of P0064.

MS (ESI, m/e) 414(M+Na)

Preparation 51



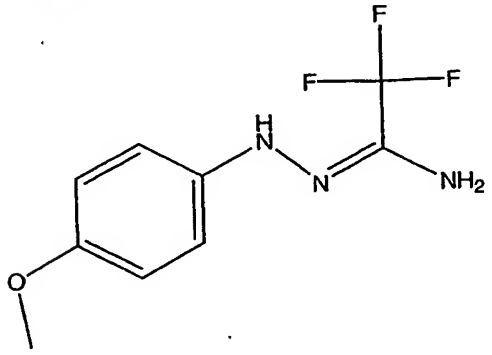
(P0051)

P0051 was obtained according to a similar manner to that of P0065.

1H NMR (CDCl3, ppm) d 3.83(3H, s), 5.05(2H, s), 6.80-7.05(4H, m), 7.18-7.55(10H, m),

MS (ESI, m/e) 374(M+1)

Preparation 52

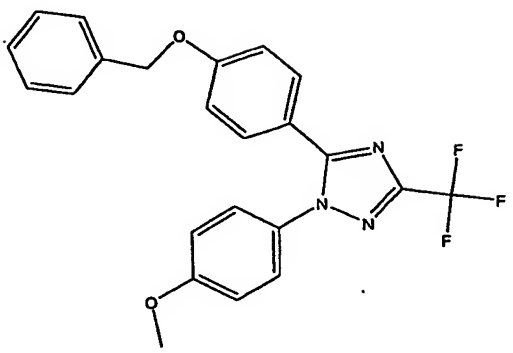


(P0052)

P0052 was obtained according to a similar manner to that of P0066.

MS (ESI, m/e) 234(M+1)

Preparation 53



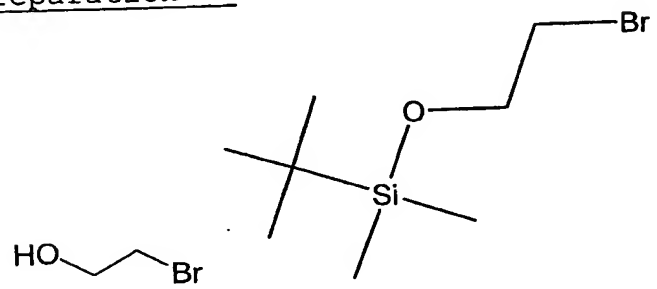
(P0053)

P0053 was obtained according to a similar manner to that of P0067.

1H NMR (CDCl3, ppm) d 3.86(3H, s), 5.07(2H, s), 6.85-7.05(4H, m), 7.20-7.58(9H, m),

MS (ESI, m/e) 426(M+1)

Preparation 54

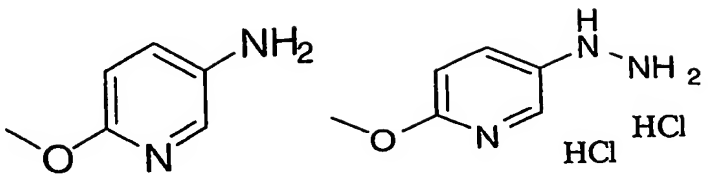


(P0054-0) (P0054)

To a solution of P0054-0 (5.0g) and imidazole (3.3g) in DMF (40ml) was added portionwise tert-butyldimethylsilyl chloride (TBDMSCl) (6.69g) at room temperature. After stirring overnight, water and hexane was added. The aqueous layer was separated and extracted twice with hexane. The combined organic layer was washed with water (twice) and brine, dried over MgSO4, filtered and evaporated under reduced pressure to give 9.49g (98.3%) of P0054.

IR (film): 2952.5, 2935.1, 1467.6, 1255.4, 1124.3, 1097.3, 838.9, 777.2 cm-1.

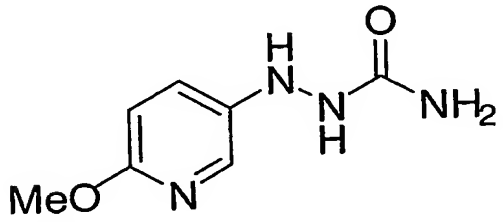
Preparation 55



(P0055-0) (P0055)

To the solution of P0055-0 (63.4 g, 511 mmol) in 500 ml of conc.HCl at -10℃ under N2, added NaNO2 (37 g, 536 mmol) in 100 ml of water dropwise (about 15min. required), kept the temperature between -10 to 15℃ for 15 more min. Then added Tin(II) chloride dihydrate (288 g, 1.28 mol) in 150 ml of conc.HCl dropwise between -10 to -15℃ (about 30 min. required). After added 100 ml of conc.HCl and 100 ml of water, stirred 1 hour at -10℃ and collected by filtration , washed with Et2O (500 ml at 3 times). Then precipitate was slurried in 500 ml of Et2O, washed with 500 ml of methanol and 500 ml of Et2O, and air dried. (43.7 g, 40% yield). 1H NMR (DMSO-d6, ppm) d 3.82 (3H, s), 6.84 (1H, d, J=9.0 Hz), 7.57 (1H, dd, J=9.0, 2.9 Hz), 7.98 (1H, d, J=2.9 Hz), 7.87-8.15 (1H, m), 10.3 (2H, bs),

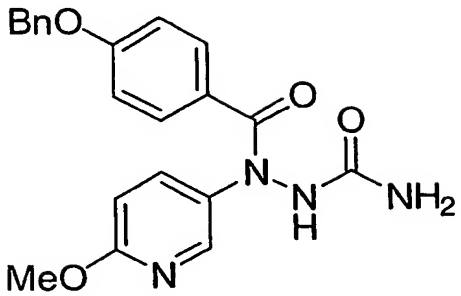
Preparation 56



(P0056)

P0056 was obtained according to a similar manner to that of P0063. 1H NMR (DMSO-d6, ppm) d 3.75 (3H, s), 5.99 (2H, bs), 6.68 (1H, d, J=8.8 Hz), 7.12 (1H, dd, J=8.8, 2.9 Hz), 7.41 (1H, bs), 7.60 (1H, d, J=2.8 Hz), 7.77 (1H, s),
MS (ESI, m/e) 205 (M+Na)

Preparation 57



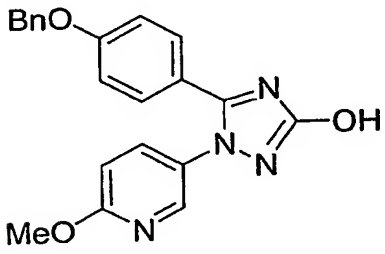
(P0057)

To a suspension of P0056 (200 mg, 1.1mmol) and pyridine (0.1 ml, 1.32 mmol) in 2 ml of dichloromethane and then 4-benzyloxybenzoylchloroide (325 mg, 1.32 mmol) was added under ice bath cooling. The mixture was stirred at room temperature for 2.5 hours and added 40 ml of water. After vigorous shaking, an insoluble material was isolated by filtration, washed with water and toluene and dried in vacuo (330 mg, 76.6% yield).

1H NMR (DMSO-d6, ppm) d 3.83(3H, s), 5.14(2H, s), 6.19(1H, bs), 6.84(1H, bd, J=8.8 Hz), 7.02(2H, bd, J=8.7 Hz), 7.28-7.62(7H, m), 7.65-7.80(1H, m), 8.16(1H, bs), 9.00(1H, bs),

MS (ESI, m/e) 415(M+Na)

Preparation 58



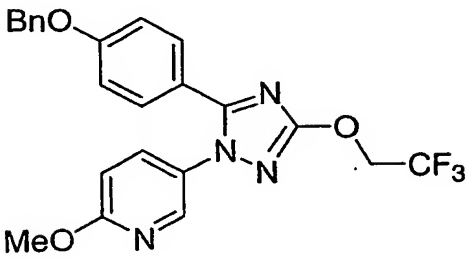
(P0058)

A mixture of P0057 (300 mg, 0.766 mmol) in 1 ml of ethanol and sodium hydroxide (46 mg, 1.15 mmol) in 1ml of water was stirred at 80°C for 1 hour. After cooling, 1N-HCl was added to the solution and the mixture was adjusted pH to ca. 4. A generated precipitate was isolated by filtration, washed with water and ethyl acetate, dried in vacuo (240 mg, 84% yield).

1H NMR (DMSO-d6, ppm) d 3.89(3H, s), 5.16(2H, s), 6.93(1H, d, J=8.9 Hz), 7.04(2H, d, J=8.8 Hz), 7.29-7.55(8H, m), 7.75(1H,

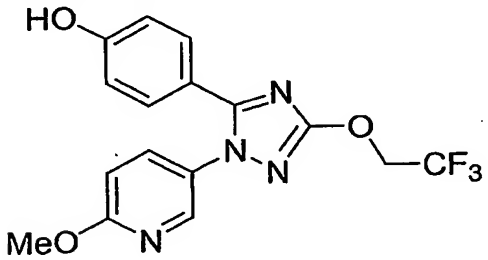
dd, J=8.8,2.6 Hz), 8.19(1H, d, J=2.6 Hz),
MS (ESI, m/e) 375(M+1)

Preparation 59



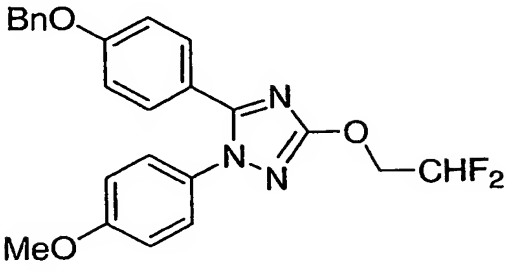
(P0059)
P0059 was obtained according to a similar manner to that of P0040.
1H NMR (CDCl3, ppm) d 3.85(3H, s), 4.74(2H, q, J=8.3 Hz), 5.06(2H, s), 6.85-7.00(4H, m), 7.21-7.54(9H, m),
MS (ESI, m/e) 456(M+1)

Preparation 60



(P0060)
10% Pd/C (50% wet, 500 mg) and P0059 (2.3 g, 5.04 mmol) in 20 ml of methanol were stirred under a hydrogen gas atmosphere at room temperature for 3.5 hours. After filtration through a selite pad, the reaction mixture was evaporated in vacuo to give P0060 (2.0 g, 108.4% yield).
1H NMR (DMSO-d6, ppm) d 3.90(3H, s), 5.00(2H, q, J=8.9 Hz), 6.71-6.82(2H, m), 6.96(1H, d, J=9.1 Hz), 7.22-7.37(2H, m), 7.80(1H, dd, J=8.8,2.8 Hz), 8.23(1H, d, J=2.4 Hz),
MS (ESI, m/e) 367(M+1)

Preparation 61



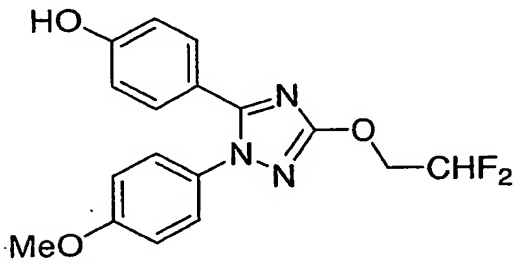
(P0061)

P0061 was obtained according to a similar manner to that of P0040 (2.1 g, 89% yield).

1H NMR (CDCl3, ppm) d 3.85(3H, s), 4.54(2H, dt, J=13.1,4.4 Hz), 5.06(2H, s), 6.17(1H, tt, J=55.3,4.4 Hz), 6.83-6.98(3H, m), 7.21-7.49(10H, m),

MS (ESI, m/e) 438(M+1)

Preparation 62



(P0062)

P0062 was obtained according to a similar manner to that of P0043 (1.5 g, 94.5% yield).

1H NMR (CDCl3, ppm) d 3.85(3H, s), 4.53(2H, dt, J=13.0,4.0 Hz), 6.17(1H, tt, J=55.2,4.5 Hz), 6.15(1H, s), 6.67-6.80(2H, m), 6.86-7.00(2H, m), 7.18-7.40(4H, m),

MS (ESI, m/e) 348(M+1)

Preparation 63

Under ice-bath cooling, potassium cyanate (1.71 g, 21.1 mmol) was added to a suspension of 4-methoxyphenylhydrazine hydrochloride (3.35 g, 19.2 mmol) in water (40 mL). The mixture was stirred for 1 hour at the same temperature. And then the mixture was warmed to room temperature and stirred for 12 hours.

An insoluble material was isolated by filtration, washed with water, and dried in vacuo to give 2-(4-methoxyphenyl)hydrazinecarboxamide (2.45 g, 70.5% yield)(P0063).

1H NMR (DMSO-d6, ppm) δ 7.64(s, 1H), 7.26(s, 1H), 6.78(d, J = 8.8 Hz, 2H), 6.67(d, J = 8.8 Hz, 2H), 5.90(s, 2H), 3.66(s, 3H)

MS (ESI, m/e) 223(M+1+MeCN)

Preparation 64

To a suspension of 2-(4-methoxyphenyl)hydrazinecarboxamide (1.81 g, 9.99 mmol) in 20 mL of toluene, pyridine (1.01 mL, 12.5 mmol) and then a solution of 4-methoxybenzoyl chloride (2.13 g, 12.5 mmol) in 10 mL of toluene were added. The mixture was refluxed with stirring for 1 hour. After cooling, 500 mL of ethyl acetate - tetrahydrofuran (9:1) and 100 mL of water were added to the mixture. After vigorous shaking, an insoluble material was isolated by filtration and dried in vacuo to give 2-(4-methoxybenzoyl)-2-(4-methoxyphenyl)hydrazinecarboxamide (1.95 g, 61.9% yield)(P0064).

1H NMR (DMSO-d6, ppm) δ 8.86(br s, 1H), 7.49(br d, J = 7.4 Hz, 2H), 7.28(br s, 2H), 6.89(m, 4H), 3.77(s, 3H), 3.73(s, 3H)

MS (ESI, m/e) 316(M+1)

Preparation 65

A mixture of 2-(4-methoxybenzoyl)-2-(4-methoxyphenyl)-hydrazinecarboxamide (1.9 g, 6.03 mmol) in 10% potassium hydroxide solution (16 mL) - ethanol (8 mL) was heated at 60 °C for 1.5 hours. After cooling, the solvent was removed under reduced pressure. Water was added to the residue and the mixture was adjusted pH to ca. 2. A generated precipitate was isolated by filtration, washed with water, and dried in vacuo to give 1,5-bis(4-methoxyphenyl)-1H-1,2,4-triazol-3-ol (1.51 g, 84.3% yield)(P0065).

1H NMR (DMSO-d6, ppm) δ 7.32(d, J = 8.9 Hz, 2H), 7.28(d, J = 8.9 Hz, 2H), 7.01(d, J = 8.9 Hz, 2H), 6.93(d, J = 8.9 Hz, 2H), 3.80(s, 3H), 3.77(s, 3H)

MS (ESI, m/e) 298(M+1)

Preparation 66

To a solution of trifluoroacetoamidine (4.24 g, 37.8 mmol) in methanol (20 mL), were added 4-methoxyphenylhydrazine hydrochloride (4.72 g, 27 mmol) and then triethylamine (3.77 mL, 27 mmol) at room temperature. The mixture was stirred for 6 hours. The solvent was removed under reduced pressure. 20 mL of water and 50 mL of ethyl acetate - tetrahydrofuran (9:1) were added to the residue and the organic layer was separated and the aqueous layer was extracted with 50 mL of ethyl acetate - tetrahydrofuran (9:1). A combined organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was removed under reduced pressure to give 2,2,2-trifluoro-N'-(4-methoxyphenyl)ethanehydrazonamide (6.82 g, 108.2% yield) (P0066). The residue was used for the next reaction without purification.

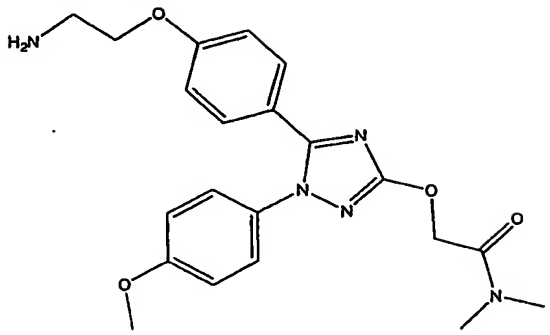
Preparation 67

To a solution of 2,2,2-trifluoro-N'-(4-methoxyphenyl)-ethanehydrazonamide (0.92 g, 3.95 mmol) in 10 mL of dioxane, were added pyridine (0.319 mL, 3.95 mmol) and a solution of 4-methoxybenzoyl chloride (673 mg, 3.95 mmol) in 3 mL of dioxane. The mixture was refluxed with stirring for 12 hours. The solvent was removed under reduced pressure. 50 mL of dichloromethane and 20 mL of 0.1 N hydrochloric acid were added to the residue and the organic layer was separated. The aqueous layer was extracted with 50 mL of dichloromethane. A combined organic layer was washed with 0.1 N hydrochloric acid and brine and dried over magnesium sulfate. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (toluene - ethyl acetate 9:1) and then recrystallized with diisopropyl ether - hexane to give pale brown needle of 1,5-bis(4-methoxyphenyl)-3- (trifluoromethyl)-1H-1,2,4-triazole (0.67 g, 48.6% yield) (P0067).

1H NMR (DMSO-d6, ppm) δ 7.45 (t, J = 8.9 Hz, 4H), 7.09(d, J = 8.9 Hz, 2H), 6.98(d, J = 8.9 Hz, 2H), 3.83(s, 3H), 3.78(s, 3H)

MS (ESI, m/e) 350(M+1)

Example 44



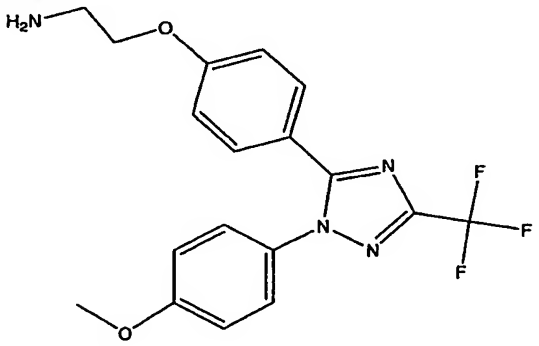
(E0044)

E0044 was obtained according to a similar manner to that of Example 126.

1H NMR (CDCl3, ppm) d 3.00(3H,), 2.99-3.17(5H,), 3.84(3H,), 3.98(2H, t, J=5.1 Hz), 5.01(2H, s), 6.75-6.98(4H, m), 7.18-7.33(2H, m), 7.35-7.47(2H, m),

MS (ESI, m/e) 412(M+1)

Example 45



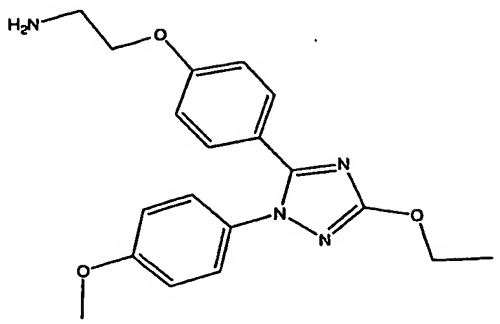
(E0045)

E0045 was obtained according to a similar manner to that of Example 126.

1H NMR (CDCl3, ppm) d 3.09(2H, t, J=5.1 Hz), 3.87(3H, s), 4.00(2H, t, J=5.1 Hz), 6.79-7.10(4H, m), 7.22-7.58(4H, m),

MS (ESI, m/e) 379(M+1)

Example 46

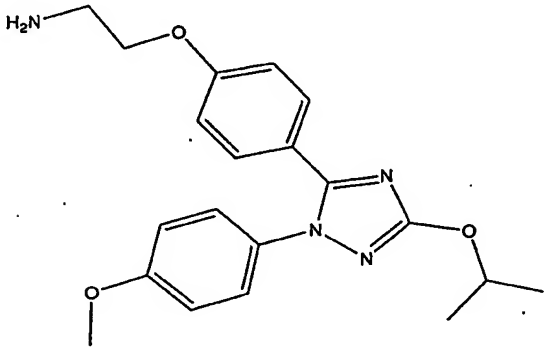


(E0046)

E0046 was obtained according to a similar manner to that of Example 126.

1H NMR (CDCl3, ppm) d 1.45(3H, t, J=7.0 Hz), 3.07(2H, t, J=5.1 Hz), 3.84(3H, s), 3.98(2H, t, J=5.1 Hz), 4.39(2H, q, J=7.0 Hz), 6.78-6.98(4H, m), 7.22-7.33(2H, m), 7.35-7.49(2H, m),
MS (ESI, m/e) 355(M+1)

Example 47

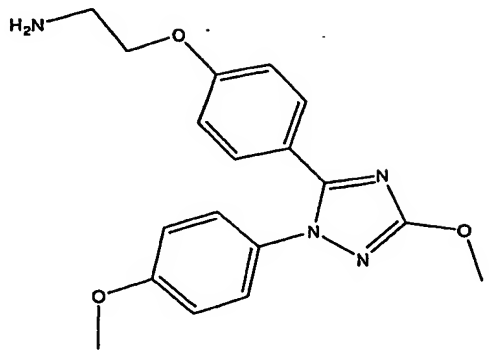


(E0047)

E0047 was obtained according to a similar manner to that of Example 126.

1H NMR (CDCl3, ppm) d 1.43(6H, d, J=6.2 Hz), 3.08(2H, t, J=5.1 Hz), 3.84(3H, s), 3.98(2H, t, J=5.1 Hz), 5.02(1H, 7th, J=6.1 Hz), 6.75-7.00(4H, m), 7.20-7.35(2H, m), 7.35-7.49(2H, m),
MS (ESI, m/e) 369(M+1)

Example 48

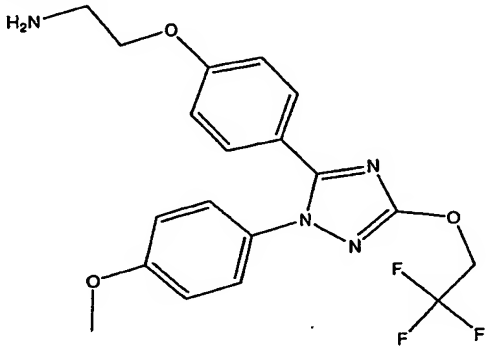


(E0048)

E0048 was obtained according to a similar manner to that of Example 126.

1H NMR (CDCl3, ppm) d 3.08(2H, t, J=5.2 Hz), 3.84(3H, s), 3.98(2H, t, J=5.1 Hz), 4.05(3H, s), 6.79-7.00(4H, m), 7.20-7.35(2H, m), 7.35-7.49(2H, m),
MS (ESI, m/e) 341(M+1)

Example 49

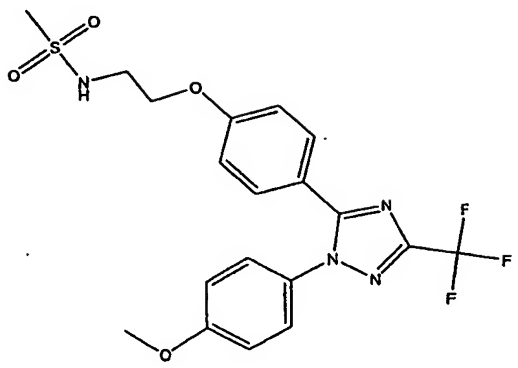


(E0049)

E0049 was obtained according to a similar manner to that of Example 126.

1H NMR (CDCl3, ppm) d 3.08(2H, t, J=5.1 Hz), 3.85(3H, s), 3.99(2H, t, J=5.1 Hz), 4.74(2H, q, J=8.3 Hz), 6.78-7.00(4H, m), 7.18-7.35(2H, m), 7.35-7.48(2H, m),
MS (ESI, m/e) 409(M+1)

Example 50

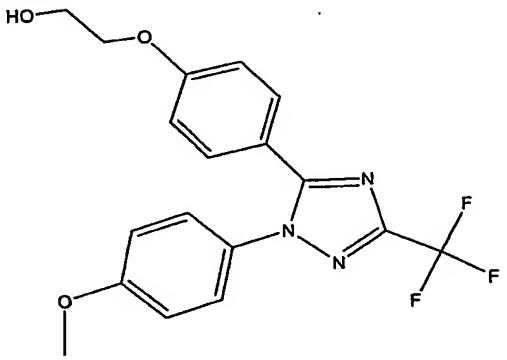


(E0050)

E0050 was obtained according to a similar manner to that of Example 148.

1H NMR (CDCl3, ppm) d 3.02(3H, s), 3.55(2H, q, J=5.4 Hz), 3.87(3H, s), 4.11(2H, t, J=5.0 Hz), 4.81(1H, bt, J=5.8 Hz), 6.75-6.90(2H, m), 6.90-7.05(2H, m), 7.20-7.40(2H, m), 7.40-7.59(2H, m),
MS (ESI, m/e) 457(M+1)

Example 51

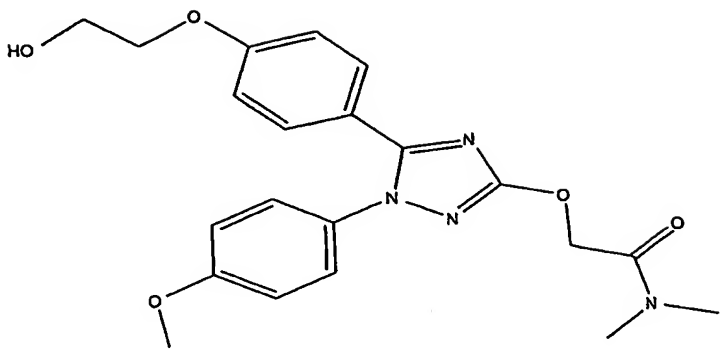


(E0051)

E0051 was obtained according to a similar manner to that of Example 145.

1H NMR (DMSO-d6, ppm) d 3.62-3.78(2H, m), 3.83(3H, s), 3.93-4.10(2H, m), 4.88(1H, t, J=5.5 Hz), 6.90-7.03(2H, m), 7.03-7.18(2H, m), 7.35-7.58(4H, m),
MS (ESI, m/e) 380(M+1)

Example 52



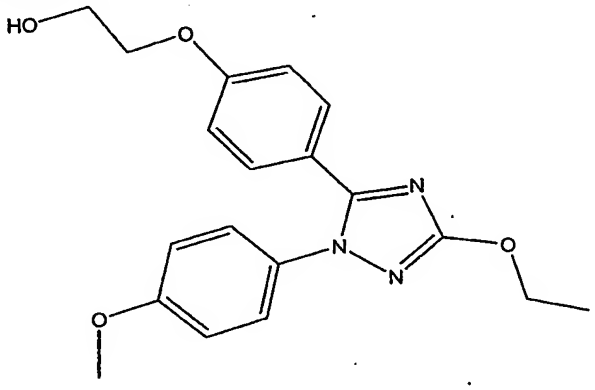
(E0052)

E0052 was obtained according to a similar manner to that of Example 145.

1H NMR (CDCl3, ppm) d 2.98(3H, s), 3.07(3H, s), 3.84(3H, s), 3.90-4.01(2H, m), 4.02-4.15(2H, m), 5.00(2H, s), 6.75-6.97(4H, m), 7.19-7.30(2H, m), 7.31-7.57(2H, m),

MS (ESI, m/e) 413(M+1)

Example 53



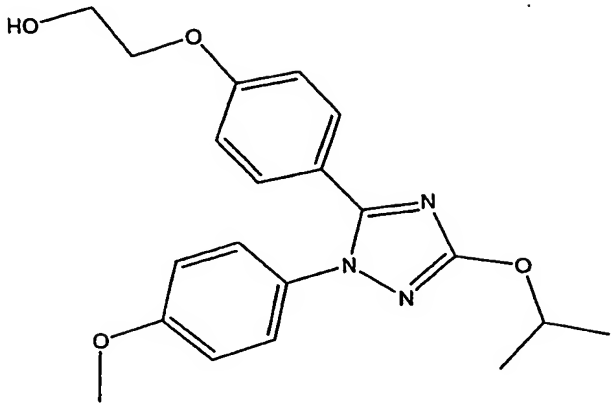
(E0053)

E0053 was obtained according to a similar manner to that of Example 145.

1H NMR (CDCl3, ppm) d 1.45(3H, t, J=7.0 Hz), 3.84(3H, s), 3.92-4.00(2H, m), 4.02-4.11(2H, m), 4.39(2H, q, J=7.0 Hz), 6.80-6.88(2H, m), 6.89-6.97(2H, m), 7.22-7.31(2H, m), 7.38-7.48(2H, m),

MS (ESI, m/e) 356(M+1)

Example 54



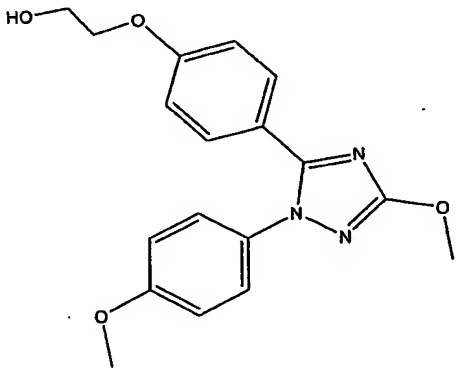
(E0054)

E0054 was obtained according to a similar manner to that of Example 145.

1H NMR (CDCl3, ppm) d 1.43(6H, d, J=6.1 Hz), 2.15(1H, t, J=6.2 Hz), 3.84(3H, s), 3.89-4.01(2H, m), 4.01-4.13(2H, m), 5.02(1H, 7th, J=6.1Hz), 6.77-6.99(4H, m), 7.20-7.35(2H, m), 7.37-7.50(2H, m),

MS (ESI, m/e) 370(M+1)

Example 55



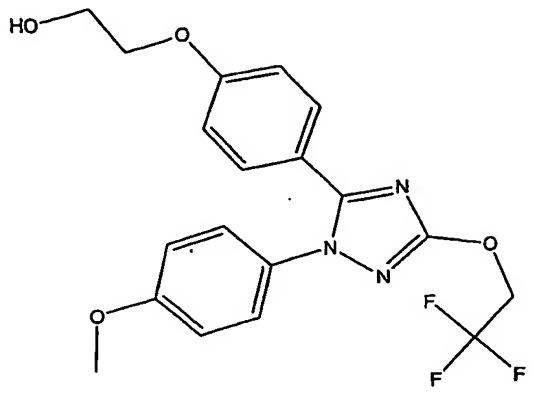
(E0055)

E0055 was obtained according to a similar manner to that of Example 145.

1H NMR (CDCl3, ppm) d 3.84(3H, s), 3.97-4.00(2H, m), 4.00-410(5H, m), 6.78-6.87(2H, m), 6.89-6.99(2H, m), 7.20-7.33(2H, m), 7.50-7.48(2H, m),

MS (ESI, m/e) 342(M+1)

Example 56



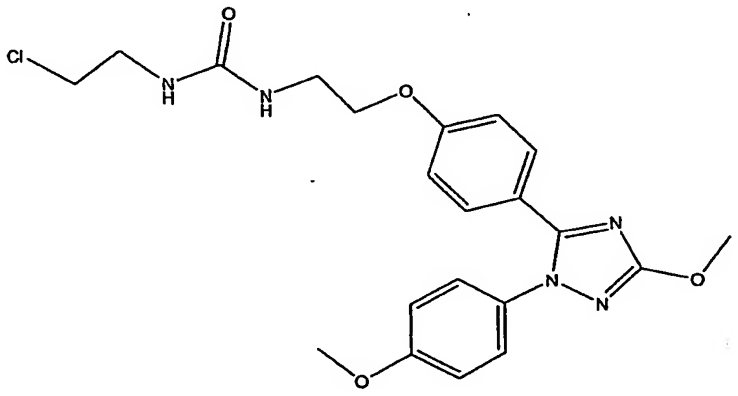
(E0056)

E0056 was obtained according to a similar manner to that of Example 145.

1H NMR (CDCl3, ppm) d 3.85(3H, s), 3.90-4.03(2H, m), 4.05-4.17(2H, m), 4.74(2H, q, J=8.2 Hz), 6.79-7.00(4H, m), 7.21-7.32(2H, m), 7.38-7.49(2H, m),

MS (ESI, m/e) 410(M+1)

Example 57

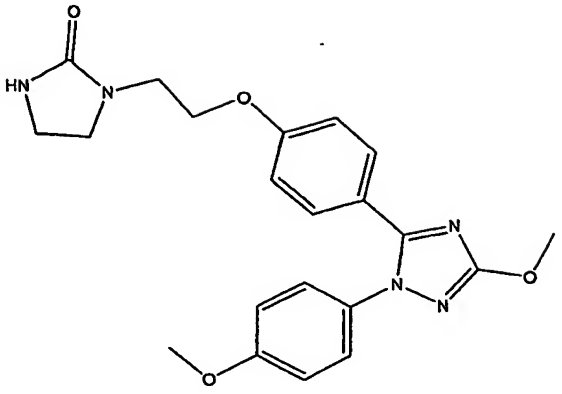


(E0057)

2-Chloroethyl isocyanate (124 mg, 1.32 mmol) was added to a solution of E0048 (200 mg, 0.881 mmol) in 1 ml of toluene. The mixture was stirred for 15 minutes at room temperature. An insoluble material was isolated by filtration, washed with toluene, and dried in vacuo (250 mg, 95.4% yield) to give E0057.

MS (ESI, m/e) 446(M+1)

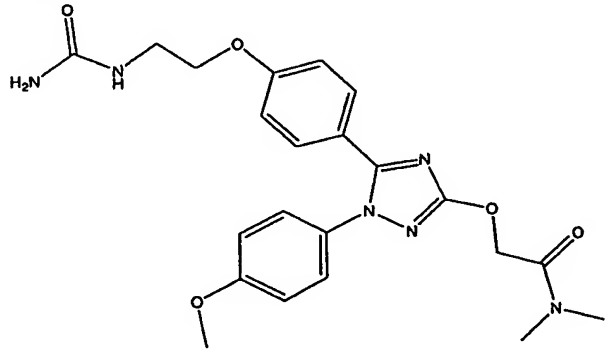
Example 58



(E0058)

Under ice-bath cooling, sodium hydride (60% dispersion, 19.7 mg, 0.493 mmol) was added to a solution of E0057 (200 mg, 0.449 mmol) in tetrahydrofuran (0.8 ml) and N,N-dimethylformamide (0.8 ml). The mixture was stirred at room temperature for 2.5 hours. The mixture was quenched with water and extracted with chloroform (x2). The combined organic layers were washed with water and brine, dried over magnesium sulfate, and evaporated to give oil. The oil was purified with column chromatography (SiO2 10 g, eluted with ethyl acetate, 50% ethyl acetate / acetone and acetone). The desired product E0058 was washed with isopropylether, isolated by filtration, and dried in vacuo (56 mg, 30.5% yield). 1H NMR (CDCl3, ppm) d 3.32-3.49(2H, m), 3.51-3.70(4H, m), 3.85(3H, s), 4.05(3H, s), 4.07-4.19(2H, m), 4.45(1H, bs), 6.75-6.89(2H, m), 6.90-7.00(2H, m), 7.20-7.36(2H, m), 7.37-7.50(2H, m), MS (ESI, m/e) 410(M+1)

Example 59



(E0059)

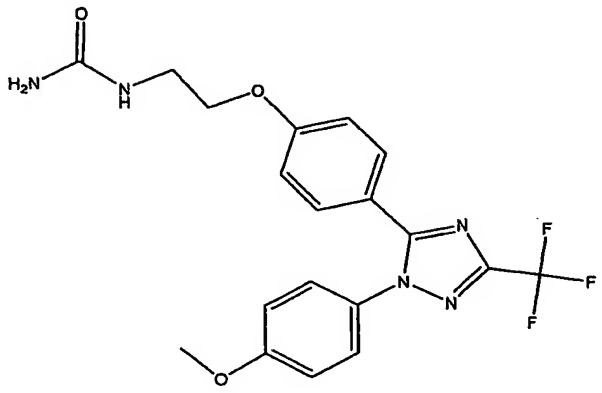
E0059 was obtained according to a similar manner to that of Example

127.

1H NMR (DMSO-d6, ppm) d 2.84(3H, s), 2.96(3H, s), 3.25-3.40(2H, m), 3.80(3H, s), 3.95(2H, t, J=5.5 Hz), 5.00(2H, s), 5.52(2H, s), 6.15(1H, bt, J=5.6 Hz), 6.89-7.08(4H, m), 7.21-7.39(4H, m),

MS (ESI, m/e) 455(M+1)

Example 60



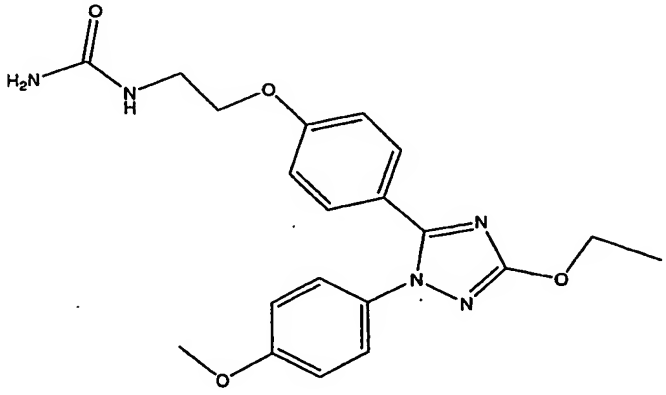
(E0060)

E0060 was obtained according to a similar manner to that of Example 127.

1H NMR (CDCl3, ppm) d 3.60(2H, bq, J=5.3 Hz), 3.87(3H, s), 4.05(2H, bt, J=4.9 Hz), 4.38(2H, bs), 4.82-5.00(1H, m), 6.84(2H, d, J=8.8 Hz), 6.96(2H, d, J=8.9 Hz), 7.30(2H, d, J=9.0 Hz), 7.46(2H, d, J=8.9 Hz),

MS (ESI, m/e) 422(M+1)

Example 61



(E0061)

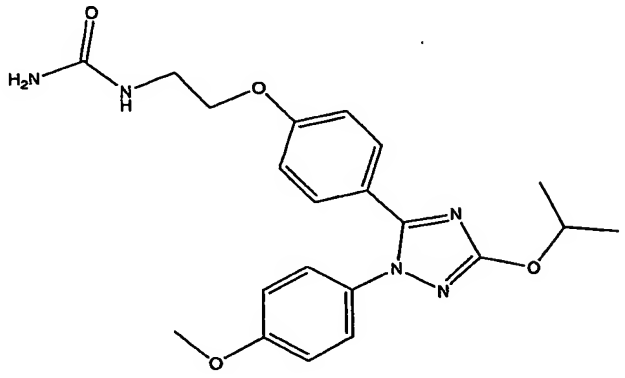
E0061 was obtained according to a similar manner to that of Example

127.

1H NMR (DMSO-d6, ppm) d 1.35(3H, t, J=7.0 Hz), 3.28-3.39(2H, m), 3.80(3H, s), 3.95(2H, t, J=5.5 Hz), 4.29(2H, q, J=7.0 Hz), 5.52(2H, s), 6.15(1H, bt, J=5.5 Hz), 6.89-7.07(4H, m), 7.25-7.39(4H, m),

MS (ESI, m/e) 398(M+1)

Example 62



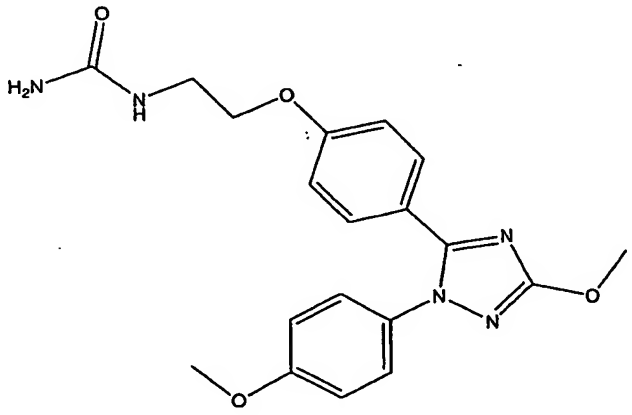
(E0062)

E0062 was obtained according to a similar manner to that of Example 127.

1H NMR (CDCl3, ppm) d 1.42(6H, d, J=6.2 Hz), 3.55(2H, q, J=5.3 Hz), 3.84(3H, s), 3.97(2H, t, J=5.1 Hz), 4.57(2H, bs), 5.01(1H, 7th, J=6.1 Hz), 5.36(1H, bt, J=5.9 Hz), 6.76(2H, d, J=8.8 Hz), 6.84-7.00(2H, m), 7.17-7.35(2H, m), 7.35-7.49(2H, m),

MS (ESI, m/e) 412(M+1)

Example 63



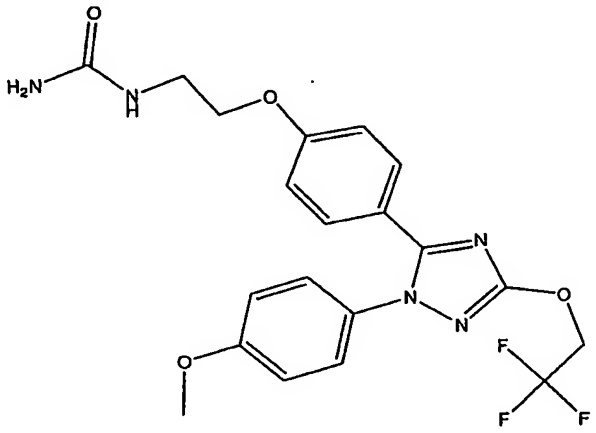
(E0063)

E0063 was obtained according to a similar manner to that of Example 127.

1H NMR (CDCl3, ppm) d 3.55(2H, q, J=5.4 Hz), 3.84(3H, s), 3.96(2H, t, J=5.1 Hz), 4.04(3H, s), 4.66(2H, bs), 5.51(1H, bt, J=5.7 Hz), 6.68-6.83(2H, m), 6.85-7.00(2H, m), 7.17-7.30(2H, m), 7.30-7.47(2H, m),

MS (ESI, m/e) 384(M+1)

Example 64



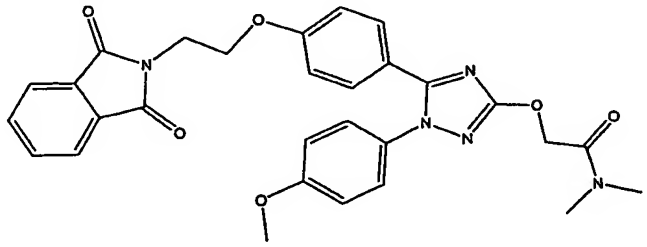
(E0064)

E0064 was obtained according to a similar manner to that of Example 127.

1H NMR (DMSO-d6, ppm) d 3.20-3.41(2H, m), 3.81(3H, s), 3.95(2H, t, J=5.5 Hz), 4.99(2H, q, J=8.9 Hz), 5.52(2H, bs), 6.15(1H, bt, J=5.5 Hz), 6.90-7.10(4H, m), 7.28-7.42(4H, m),

MS (ESI, m/e) 452(M+1)

Example 65



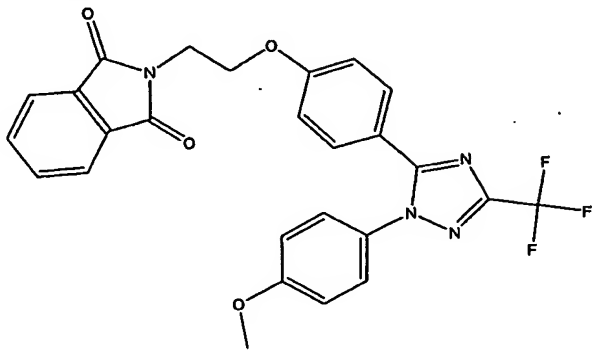
(E0065)

E0065 was obtained according to a similar manner to that of Example 125.

1H NMR (CDCl3, ppm) d 2.99(3H, s), 3.06(3H, s), 4.03-4.15(2H, m), 4.15-4.28(2H, m), 4.99(2H, s), 6.70-6.82(2H, m), 6.82-6.97(2H, m), 7.17-7.30(2H, m), 7.30-7.42(2H, m), 7.68-7.80(2H, m), 7.80-7.91(2H, m),

MS (ESI, m/e) 542(M+1)

Example 66



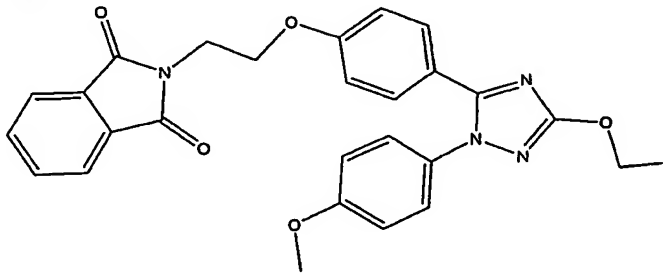
(E0066)

E0066 was obtained according to a similar manner to that of Example 125.

1H NMR (DMSO-d6, ppm) d 3.82(3H, s), 3.96(2H, bt, J=5.7 Hz), 4.24(2H, bt, J=5.7 Hz), 6.94(2H, d, J=8.9 Hz), 7.07(2H, d, J=9.0 Hz), 7.35-7.55(4H, m), 7.75-7.98(4H, m),

MS (ESI, m/e) 509(M+1)

Example 67



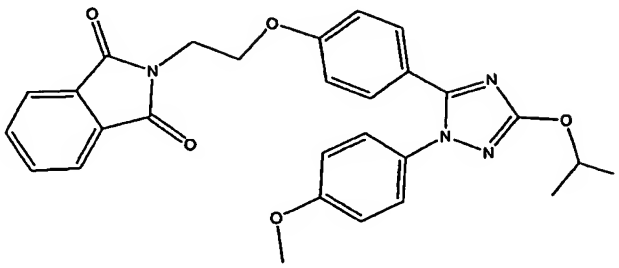
(E0067)

E0067 was obtained according to a similar manner to that of Example 125.

1H NMR (CDCl3, ppm) d 1.44(3H, t, J=7.0 Hz), 3.83(3H, s), 4.04-4.17(2H, m), 4.17-4.28(2H, m), 4.38(2H, q, J=7.0 Hz), 6.70-6.83(2H, m), 6.85-6.95(2H, m), 7.17-7.30(2H, m),

7.31-7.42(2H, m), 7.68-7.79(2H, m), 7.80-7.94(2H, m),
MS (ESI, m/e) 485(M+1)

Example 68

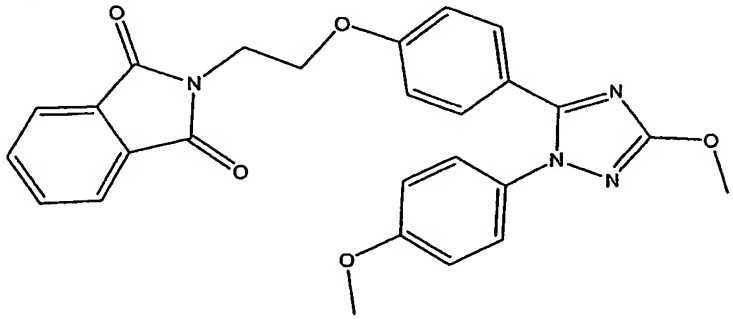


(E0068)

E0068 was obtained according to a similar manner to that of Example 125.

1H NMR (CDCl3, ppm) d 1.42(6H, d, J=6.1 Hz), 3.83(3H, s), 4.07-4.19(2H, m), 4.19-4.29(2H, m), 5.01(1H, 7th, J=6.1 Hz), 6.71-6.84(2H, m), 6.85-6.97(2H, m), 7.18-7.30(2H, m), 7.31-7.45(2H, m), 7.69-7.80(2H, m), 7.80-7.91(2H, m),
MS (ESI, m/e) 499(M+1)

Example 69

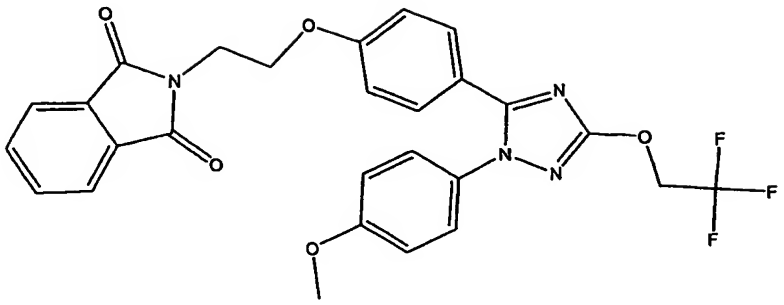


(E0069)

E0069 was obtained according to a similar manner to that of Example 125.

1H NMR (CDCl3, ppm) d 3.83(3H, s), 4.03(3H, s), 4.03-4.29(4H, m), 6.72-6.87(2H, m), 6.87-6.99(2H, m), 7.19-7.32(2H, m), 7.33-7.45(2H, m), 7.68-7.80(2H, m), 7.80-7.92(2H, m),
MS (ESI, m/e) 471(M+1)

Example 70



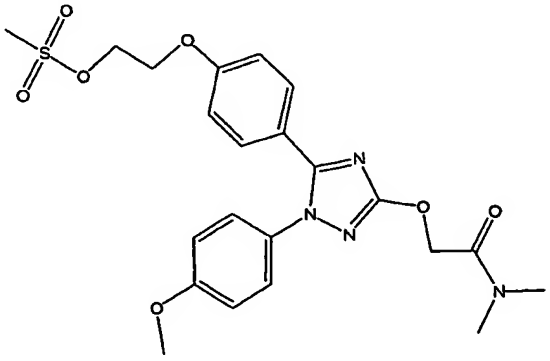
(E0070)

E0070 was obtained according to a similar manner to that of Example 125.

1H NMR (CDCl3, ppm) d 3.84(3H, s), 4.10(2H, t, J=5.2 Hz), 4.22(2H, t, J=4.9 Hz), 4.73(2H, q, J=8.4 Hz), 6.76-6.85(2H, m), 6.85-6.99(2H, m), 7.24(2H, dd, J=2.4,7.0 Hz), 7.38(2H, d, J=6.7 Hz), 7.67-7.95(4H, m),

MS (ESI, m/e) 539(M+1)

Example 71

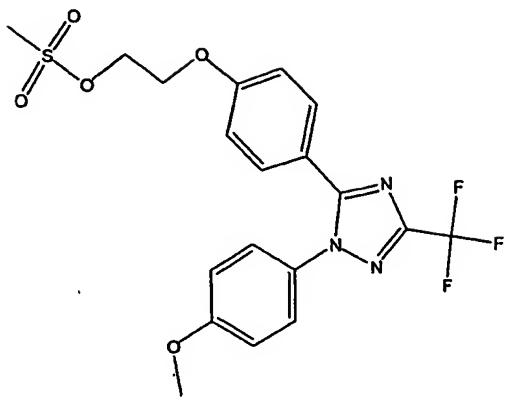


(E0071)

E0071 was obtained according to a similar manner to that of Example 124.

MS (ESI, m/e) 491(M+1)

Example 72

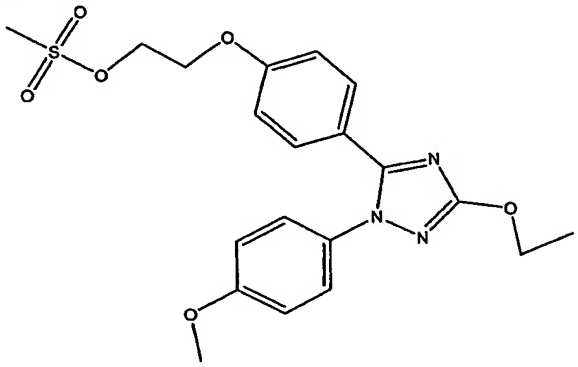


(E0072)

E0072 was obtained according to a similar manner to that of Example 124.

MS (ESI, m/e) 458 (M+1)

Example 73

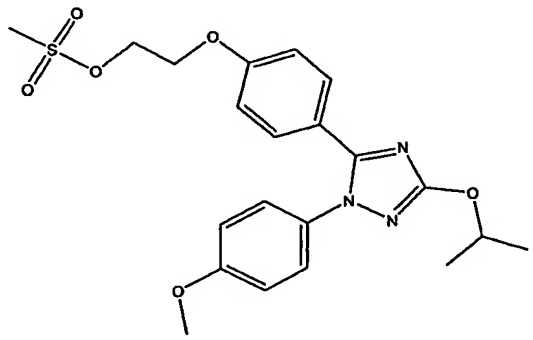


(E0073)

E0073 was obtained according to a similar manner to that of Example 124.

MS (ESI, m/e) 434 (M+1)

Example 74

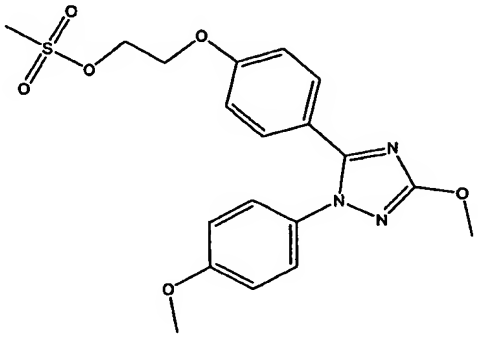


(E0074)

E0074 was obtained according to a similar manner to that of Example 124.

MS (ESI, m/e) 448(M+1)

Example 75

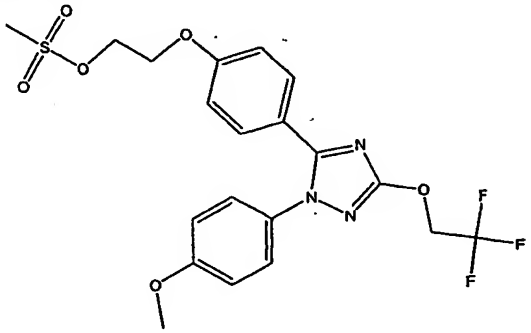


(E0075)

E0075 was obtained according to a similar manner to that of Example 124.

MS (ESI, m/e) 420(M+1)

Example 76

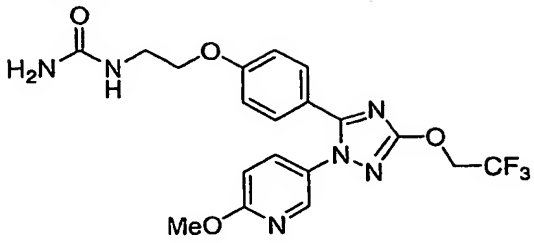


(E0076)

E0076 was obtained according to a similar manner to that of Example 124.

MS (ESI, m/e) 488(M+1)

Example 77



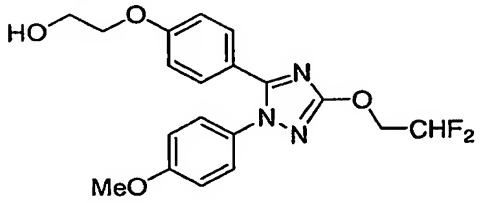
(E0077)

To a solution of P0060 in dimethylformamide (1 ml), potassium carbonate (453 mg, 3.28 mmol), potassium iodide (90 mg, 0.546 mmol) and N-(2-bromoethyl)urea (274 mg, 1.64 mmol) were added. The mixture was heated at 120℃ for 3 hours. Then N-(2-bromoethyl)urea (91 mg, 54 mmol) was added to the mixture per 1 hour at 5 times. After cooling, ethyl acetate and water were poured into the mixture. The organic layer was separated and dried over magnesium sulfate. The solvent was removed under reduced pressure. The residue was purified by silicagel chromatografy (dichloromethane-methanol 20:1). The desired product E0077 was isolated by filtration ,washed with isopropylether and dried in vacuo. (100 mg, 40.5% yield)

1H NMR (DMSO-d6, ppm) d 3.22-3.47(2H, m), 3.90(3H, s), 3.96(2H, t, J=5.5 Hz), 5.01(2H, q, J=8.8 Hz), 5.53(2H, bs), 6.16(1H, bt, J=5.5 Hz), 6.91-7.08(3H, m), 7.39(2H, d, J=8.7 Hz), 7.82(1H, dd, J=8.8, 2.7 Hz), 8.26(1H, d, J=2.5 Hz),

MS (ESI, m/e) 353(M+1)

Example 78



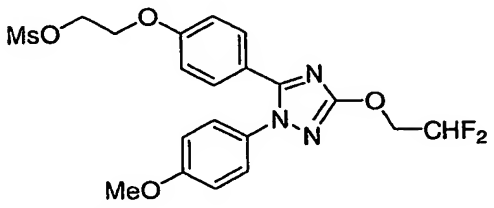
(E0078)

E0078 was obtained according to a similar manner to that of Example 145.

1H NMR (CDCl3, ppm) d 2.09(1H, t, J=6.2 Hz), 3.85(3H, s),

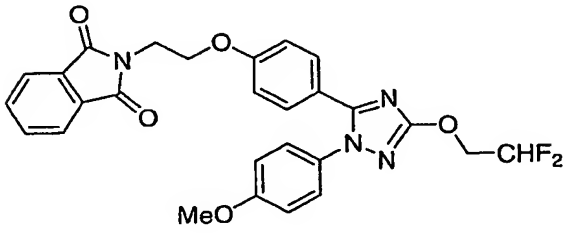
3.90-4.01(2H, m), 4.05-4.13(2H, m), 4.54(2H, dt, J=13.1,4.4 Hz), 6.18(1H, tt, J=55.2,4.4 Hz), 6.79-7.00(4H, m), 7.22-7.31(2H, m), 7.35-7.49(2H, m),
(ESI, m/e) 392(M+1)

Example 79



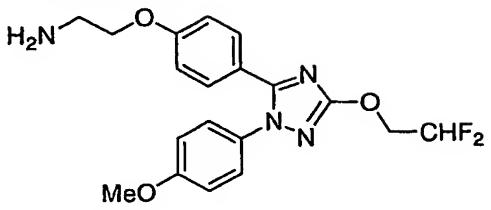
(E0079)
E0079 was obtained according to a similar manner to that of Example 124.
MS (ESI, m/e) 470(M+1)

Example 80



(E0080)
E0080 was obtained according to a similar manner to that of Example 125.
1H NMR (CDCl3, ppm) d 3.84(3H, s), 4.05-4.17(2H, m), 4.18-4.29(2H, m), 4.53(2H, td, J=13.0,4.3 Hz), 6.19(2H, tt, J=55.3,4.4 Hz), 6.75-6.88(2H, m), 6.89-6.99(2H, m), 7.18-7.32(2H, m), 7.32-7.45(2H, m), 7.65-7.80(2H, m), 7.80-7.90(2H, m),
MS (ESI, m/e) 521(M+1)

Example 81



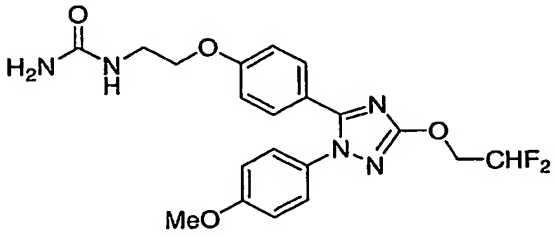
(E0081)

E0081 was obtained according to a similar manner to that of Example 126.

1H NMR (CDCl3, ppm) d 3.08(2H, t, J=5.2 Hz), 3.85(3H, s), 3.99(2H, t, J=5.1 Hz), 4.54(2H, td, J=13.1,4.3 Hz), 6.18(1H, tt, J=55.2,4.3 Hz), 6.77-6.89(2H, m), 6.89-7.00(2H, m), 7.21-7.32(2H, m), 7.35-7.49(2H,),

MS (ESI, m/e) 391(M+1)

Example 82



(E0082)

To a solution of E0081 (200 mg, 0.512 mmol) in 1 ml of EtOH and 4 ml of 1N-HCl, potassium cyanate (208 mg, 2.56 mmol) was added slowly. The mixture was stirred at 50°C for 1hr. Furthermore, potassium cyanate (124 mg, 1.54 mmol) was added and stirred at same temperature for 1hr. After cooling, water and 1N-HCl were added and an insoluble material was isolated by filtration. The residue was purified by recrystallized with EtOH (1 ml) to get the white crystal of E0082 (160mg, 72.1%).

1H NMR (DMSO-d6, ppm) d 3.19-3.39(2H, m), 3.81(3H, s), 3.95(2H, bt, J=5.5 Hz), 4.56(2H, td, J=14.9,3.4 Hz), 5.52(2H, bs), 6.43(2H, tt, J=54.2,3.4 Hz), 6.09-6.23(1H, m), 6.90-7.11(4H, m), 7.27-7.41(4H, m),

MS (ESI, m/e) 434(M+1)

Preparation 68

methyl 1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)-4,5-dihydro-1H-imidazole-4-carboxylate(5 g) and manganese(IV) oxide (5.22 g) in DMF (50 ml) was stirred at 100℃ for overnight. After filtration, the reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography silica-gel eluting with (n-Hexane:AcOEt=1:1) to give methyl 1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)-1H-imidazole-4-carboxylate (4.62 g).

1HNMR (200MHz, DMSOd6): 3.75 (3H, s), 3.79 (3H, s), 5.15 (2H, s), 6.88 (2H, d, J = 9Hz), 7.1 (2H, d, J = 9Hz), 7.24 - 7.31 (4H, m), 7.34 - 7.49 (5H, m), 8.06 (1H, s),

Mass (ESI+) : 415 (M+H)+

Preparation 69

To a solution of {4-[2-(benzyloxy)ethoxy]phenyl}amine (1 g) in THF(5 ml) was added dropwise 1.0M-sodium bis(trimethylsilyl)-amide in THF(4.11 ml) at room temperature. After the mixture was stirred for 20 min, anisonitrile (0.55 g) was added. The reaction mixture was stirred for 4 hours then poured into 100ml of ice-water. The precipitate was collected by filtration, washed with diisopropyl ether to give N-{4-[2-(benzyloxy)ethoxy]phenyl}-4-methoxybenzenecarboximidamide (0.82 g) .

1HNMR (200MHz, DMSOd6): 3.33 (3H, s), 3.74 - 3.8 (2H, m), 4.1 (2H, t, J = 4.5Hz), 4.57 (2H, s), 6.07 (2H, b.s), 6.75 (2H, d, J = 8.5Hz), 6.88 - 6.98 (4H, m), 7.28 - 7.37 (5H, m), 7.92 (2H, d, J = 8.5Hz),

IR (KBr): 3485, 3375, 3060, 3032, 2991, 2931, 2908, 2868, 1886, 1621 cm-1.

Mass (ESI+) : 377 (M+H)+

Preparation 70

A mixture of N-{4-[2-(benzyloxy)ethoxy]phenyl}-4-methoxybenzenecarboximidamide (2 g) , 2-chlorocyanoethylene

(0.64 ml) and N,N-diisopropylethylamine (1.39 ml) in THF (20 ml) was stirred at reflux condition for overnight. After cooling to room temperature, the reaction mixture was poured into H2O and extracted with AcOEt. The organic layer was washed with H2O and brine, then dried over MgSO4 and evaporated in vacuo. The residue was purified by column chromatography silica-gel eluting with (n-Hexane:AcOEt=3:1) to give 1-{4-[2-(benzyloxy)ethoxy]phenyl}-2-(4-methoxyphenyl)-4,5-dihydro-1H-imidazole-4-carbonitrile (2.05 g) as an oil.
1HNMR (200MHz, DMSOd6): 3.71 - 3.75 (2H, m), 3.73 (3H, s), 3.98 - 4.19 (4H, m), 4.53 (2H, s), 5.2 (1H, dd, J = 8.5 ,10.5Hz), 6.83 - 6.95 (6H, m), 7.27 - 7.37 (7H, m),
IR (Neat) : 3057, 3035, 3006, 2931, 2871, 2243, 1606 cm-1
Mass (ESI+) : 428 (M+H)+

Preparation 71

1N aqueous sodioum hydroxide (8.98 ml) was added to a solution of methyl 1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)-1H-imidazole-4-carboxylate (1.86 g) in methanol (18 ml) and THF (18 ml). After stirring at room temperature for 2 hours, the reaction mixture was poured into water and ethyl acetate, and extracted with water. Then the water layer was acidified with 10% aqueous potassium hydrogen sulfate, extracted with ethyl acetate, dried over MgSO4 and evaporated in vacuo.The resulting precipitates were collected by filtration and washed with diisopropyl ether to give 1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)-1H-imidazole-4-carboxylic acid (1.53 g).
NMR (DMSO-d6) d; 3.75 (3H, s), 5.15 (2H, s), 6.88 (2H, d, J=8.8Hz), 7.10 (2H, d, J=8.9Hz), 7.24-7.45 (9H, m), 7.96 (1H, s) 11.0-12.5 (1H, br).
IR (KBr): 3392, 3224, 3145, 3076, 2972, 2935, 2893, 1701, 1610 cm-1.
Mass (ESI+) : 401 (M+H)+

Preparation 72

A mixture of N-[4-(benzyloxy)phenyl]-4-methoxybenzene-

carboximidamide (0.5 g) , methyl 2,3-dichloropropionate (354 mg) and N,N-diisopropylethylamine (1.05 ml) in THF (5 ml) was stirred at reflux condition for 8 hours. After cooling to room temperature, the reaction mixture was poured into H2O and extracted with AcOEt. The organic layer was washed with H2O and brine, then dried over MgSO4 and evaporated in vacuo. Resulting precipitates were collected by filtration to give methyl 1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)-4,5-dihydro-1H-imidazole-4-carboxylate (0.59 g).

1HNMR (200MHz, DMSOd6): 3.7 (3H, s), 3.74 (3H, s), 4.04 (2H, d, J = 10.5Hz), 4.8 (1H, t, J = 9.8Hz), 5.02 (2H, s), 6.83 - 6.93 (6H, m), 7.33 - 7.44 (7H, m),

Mass (ESI+) : 417 (M+H)+

Example 83

The mixture of 1-[1-[4-(2-hydroxyethoxy)phenyl]-2-(4-methoxyphenyl)-1H-imidazol-4-yl]ethanone (200 mg), O-methylhydroxylamine hydrochloride (57 mg) and pyridine (55 ml) was refluxed for 1huor. After cooling to room temperature, the reaction mixture was poured into H2O and extracted with AcOEt. The organic layer was washed with H2O and brine, then dried over MgSO4 and evaporated in vacuo. The residue was purified by column chromatography silica-gel eluting with (n-Hexane:AcOEt=1:1) to give (1E)-1-[1-[4-(2-hydroxyethoxy)phenyl]-2-(4-methoxyphenyl)-1H-imidazol-4-yl]ethanone O-methyloxime (100 mg).

1HNMR (200MHz, DMSOd6): 2.17 (3H, s), 3.69 - 3.77 (2H, m), 3.74 (3H, s), 3.86 (3H, s), 4.02 (2H, t, J = 5Hz), 4.91 (1H, t, J = 5.5Hz), 6.87 (2H, d, J = 9Hz), 7.01 (2H, d, J = 9Hz), 7.23 (2H, d, J = 3Hz), 7.27 (2H, d, J = 3Hz), 7.61 (1H, s),

IR (KBr) : 3221, 3147, 3087, 2964, 2931, 2900, 1612 cm-1

Mass (ESI+) : 382 (M+H)+

The following compound(s) was(were) obtained in a similar manner to that of Example 83.

Example 84

(1E)-1-[1-[4-(2-hydroxyethoxy)phenyl]-2-(6-methoxy-3-pyridinyl)-1H-imidazol-4-yl]-2-methyl-1-propanone O-methyloxime

1HNMR (200MHz, DMSOd6): (6H, m), 3.43 - 3.57 (1H, m), 3.72 - 3.77 (2H, m), 3.83 (3H, s), 3.88 (3H, s), 4.01 - 4.06 (2H, m), 4.91 (1H, t, J = 5.3Hz), 6.81 (1H, d, J = 10.7Hz), 7.02 - 7.06 (2H, m), 7.3 - 7.06 (2H, m), 7.55 (1/5H, s), 7.64 - 7.69 (1H, m), 8 (4/5H, s), 8.06 (1H, d, J = 2Hz),

IR (KBr) : 3398, 3330, 2970, 2935, 2871, 1647, 1610 cm-1

Mass (ESI+) : 411 (M+H)+

Example 85

A mixture of N-{4-[2-(benzyloxy)ethoxy]phenyl}-4-methoxybenzenecarboximidamide(0.8 g) ,0.91 N 3-bromobut-3-en-2-one (3.5 ml) and N,N-diisopropylethylamine (0.56 ml) in THF (3 ml) was stirred at reflux condition for overnight. After cooling to room temperature, the reaction mixture was poured into H2O and extracted with AcOEt. The organic layer was washed with H2O and brine, then dried over MgSO4 and evaporated in vacuo. The residue was dissolved into DMF (8 ml). Then manganese(IV) oxide (0.92 g) was added to the solution. The mixture was stirred at 100℃ for 4 hours. After filtration, the reaction mixture was poured into water and extracted with AcOEt, dried over MgSO4 and evaporated in vacuo. The residue was purified by column chromatography silica-gel eluting with (n-Hexane:AcOEt=3:1) to give 1-[1-{4-[2-(benzyloxy)ethoxy]phenyl}-2-(4-methoxyphenyl)-1H-imidazol-4-yl]ethanone (0.56 g) as an oil.

1HNMR (200MHz, DMSOd6): 2.48 (3H, d), 3.73 (3H, s), 3.79 (2H, t, J = 4.5Hz), 4.19 (2H, t, J = 4.5Hz), 4.56 (2H, s), 6.88 (2H, d, J = 8.5Hz), 7.05 (2H, d, J = 9Hz), 7.28 (2H, d, J = 8.5Hz), 7.324 - 7.36 (7H, m), 8.12 (1H, s),

IR (Neat) : 3838, 3807, 3745, 3645, 3612, 3128, 3062, 3033, 2933, 2870, 1732, 1674, 1614 cm-1

Mass (ESI+) : 443 (M+H)+

The following compound(s) was(were) obtained in a similar manner

to that of Example 85.

Example 86

1-[1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)-1H-imidazol-4-yl]ethanone

1HNMR (200MHz, DMSOd6): 2.47 (3H, s), 3.75 (3H, s), 5.15 (2H, s), 6.89 (2H, d, J = 9Hz), 7.11 (2H, d, J = 8.5Hz), 7.26 - 7.32 (4H, m), 7.34 - 7.49 (5H, m), 8.12 (1H, s),

IR (KBr) : 3130, 3060, 3032, 2943, 2864, 1674, 1606 cm-1

Mass (ESI+) : 399 (M+H)+

Example 87

1-[1-{4-[2-(benzyloxy)ethoxy]phenyl}-2-(4-methoxyphenyl)-1H-imidazol-4-yl]ethanone (0.56 g) and dry 20% Pd(OH)2/C (200 mg) in EtOH (10 ml) and cyclohexene (5 ml) was stirred at reflux condition for 2 hours and cooled to room temperature. After filtration, the reaction mixture was evaporated in vacuo to give 1-[1-[4-(2-hydroxyethoxy)phenyl]-2-(4-methoxyphenyl)-1H-imidazol-4-yl]ethanone (0.41 g).

1HNMR (200MHz, DMSOd6): 1.99 (3H, s), 3.65 - 3.81 (2H, m), 3.74 (3H, s), 3.97 - 4.08 (2H, m), 4.91 (1H, t, J = 5.5Hz), 6.9 (2H, d, J = 9Hz), 7.03 (2H, d, J = 9Hz), 7.28 (4H, d, J = 8.5Hz), 8.12 (1H, s),

IR (KBr) : 3278, 3136, 3066, 3003, 2964, 2931, 2843, 1736, 1670, 1612 cm-1

Mass (ESI+) : 353 (M+H)+

The following compound(s) was(were) obtained in a similar manner to that of Example 87.

Example 88

1-[1-[4-(2-hydroxyethyl)phenyl]-2-(4-methoxyphenyl)-1H-imidazol-4-yl]ethanone

1HNMR (200MHz, DMSOd6): 2.48 (3H, s), 2.78 (2H, t, J = 6.8Hz), 3.6 - 3.68 (2H, m), 3.75 (3H, s), 4.7 (1H, b.s), 6.89 (2H, d, J = 9Hz), 7.23 - 7.36 (6H, m), 8.15 (1H, s),

IR (KBr) : 3452, 3442, 3438, 3128, 3055, 2943, 2910, 2875, 2841, 1660, 1612
Mass (ESI+) : 337 (M+H)+

Example 89
[1-[4-(2-hydroxyethoxy)phenyl]-2-(4-methoxyphenyl)-1H-imidazol-4-yl](phenyl)methanone
1HNMR (200MHz, DMSOd6): 3.7 - 3.78 (2H, m), 3.75 (3H, s), 4.03 (2H, t, J = 4.8Hz), 4.91 (1H, t, J = 5.3Hz), 6.92 (2H, d, J = 9Hz), 7.04 (2H, d, J = 9Hz), 7.33 (4H, d, J = 7.5Hz), 7.518 - 7.65 (3H, m), 8.14 (1H, s), 8.28 (2H, d, J = 7Hz),
IR (KBr) : 3251, 3132, 3064, 2947, 2879, 2843, 1641, 1608 cm-1
Mass (ESI+) : 415 (M+H)+

Example 90
cyclohexyl[1-(4-hydroxyphenyl)-2-(6-methoxy-3-pyridinyl)-1H-imidazol-4-yl]methanone
1HNMR (200MHz, DMSOd6): 1.17 - 1.48 (5H, m), 1.66 - 1.84 (5H, m), 3.33 - 3.46 (1H, m), 3.84 (3H, s), 6.8-6.86 (3H, m), 7.2 (2H, d, J = 8.5Hz), 7.67 (1H, dd, J = 2.3 ,8.5Hz), 8.07 (1H, d, J = 2Hz), 8.15 (1H, s), 9.01 (1H, b.s),
IR (KBr) : 3334, 3248, 3221, 3165, 2935, 2854, 1660, 1606 cm-1
Mass (ESI+) : 378 (M+H)+

Example 91
1-[1-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1H-imidazol-4-yl]ethanone
1HNMR (200MHz, DMSOd6): 2.47 (3H, s), 3.74 (3H, s), 6.79 - 6.85 (2H, m), 6.87-6.93 (2H, m), 7.16 (2H, dt, J = 3.5 ,5.3Hz), 7.29 (2H, dt, J = 3.5 ,5Hz), 8.08 (1H, s), 8.92 (1H, b.s),
IR (KBr) : 3149, 3055, 2941, 2843, 1670, 1608 cm-1
Mass (ESI+) : 309 (M+H)+

Example 92
1-{4-[2-(benzyloxy)ethoxy]phenyl}-2-(4-methoxyphenyl)-4,5-dihydro-1H-imidazole-4-carbonitrile(2.05 g) and manganese(IV)

oxide (2.08 g) in DMF (20 ml) was stirred at 100℃ for overnight. After filtration, the reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. To the solution of the residue in DMF (20ml) phosphorus oxychloride (0.45ml) was added under stirring at 0℃. After stirring at room temperature for 1 hour, the reaction mixture was poured into saturated aqueous NaHCO3 and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography silica-gel eluting with (n-Hexane:AcOEt=1:1) to give 1-{4-[2-(benzyloxy)ethoxy]phenyl}-2-(4-methoxyphenyl)-1H-imidazole-4-carbonitrile (1.69 g).
1HNMR (200MHz, DMSOd6): 3.73 (3H, s), 3.76 - 3.8 (2H, m), 4.16 - 4.21 (2H, m), 4.56 (2H, s), 6.89 (2H, d, J = 8.5Hz), 7.06 (2H, d, J = 9Hz), 7.241 - 7.36 (9H, m), 8.39 (1H, s),
IR (KBr) : 3137, 3060, 3035, 2933, 2868, 2231, 1610 cm-1
Mass (ESI+) : 426 (M+H)+

Example 93

1N solution of cyclopentylmagnesium chloride in tetrahydrofuran (2.82 ml) was added to a solution of 1-{4-[2-(benzyloxy)ethoxy]phenyl}-2-(4-methoxyphenyl)-1H-imidazole-4-carbonitrile (0.3 g) in tetrahydrofuran (3 ml) under stirring at 0℃. After stirring at room temperature for 2 hours, the reaction mixture was poured into aqueous 10% potassium hydrogen sulfate and stirred at room temperature for 30 minutes. The mixture was alkalinized with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate, washed with H2O, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography silica-gel eluting with (n-Hexane:AcOEt=3:1) to give [1-{4-[2-(benzyloxy)ethoxy]phenyl}-2-(4-methoxyphenyl)-1H-imidazol-4-yl](phenyl)methanone (0.45 g).
1HNMR (200MHz, DMSOd6): 3.75 (3H, s), 3.76 - 3.82 (2H, m), 4.17 - 4.22 (2H, m), 4.57 (2H, s), 6.91 (2H, d, J = 8.5Hz), 7.06 (2H, d, J = 9Hz), 7.3 - 7.36 (12H, m), 8.14 (1H, s),

8.25-8.30 (2H, m),
IR (KBr) : 3028, 3062, 3032, 2931, 2868, 1691, 1643, 1624, 1612 cm-1
Mass (ESI+) : 505 (M+H)+

The following compound(s) was(were) obtained in a similar manner to that of Example 93.

Example 94

1-[1-{4-[2-(benzyloxy)ethyl]phenyl}-2-(4-methoxyphenyl)-1H-imidazol-4-yl]ethanone
1HNMR (200MHz, DMSOd6): 2.5 (3H, s), 2.93 (2H, t, J = 6.5Hz), 3.65 - 3.72 (2H, m), 3.73 (3H, s), 4.49 (2H, s), 6.84 (2H, b.s), 7.24 - 7.35 (11H, m), 8.17 (1H, s),
Mass (ESI+) : 427 (M+H)+

Example 95

[1-[4-(benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)-1H-imidazol-4-yl](cyclohexyl)methanone
1HNMR (200MHz, DMSOd6): 1.27 - 1.42 (5H, m), 1.65 - 1.84 (5H, m), 3.3 - 3.39 (1H, m), 3.84 (3H, s), 5.15 (2H, s), 6.81 (1H, d, J = 8Hz), 7.12 (2H, d, J = 8.5Hz), 7.33 - 7.49 (7H, m), 7.67 (1H, dd, J = 2.5 ,8.5Hz), 8.08 (1H, d, J = 1.5Hz), 8.19 (1H, s),
IR (KBr) : 3124, 3066, 3037, 2924, 2854, 1658, 1608 cm-1
Mass (ESI+) : 468 (M+H)+

Example 96

cyclohexyl[1-(4-hydroxyphenyl)-2-(6-methoxy-3-pyridinyl)-1H-imidazol-4-yl]methanone (500 mg), 2-chloroethanol (0.533 ml), potassium carbonate (1.1 g) and potassium iodide (1.32 g) in N,N-dimethylformamide (3 ml) was stirred at 75℃ for overnight. Then the reaction mixture was poured into water and extracted with ethyl acetate, dried over MgSO4 and evaporated in vacuo. The residue was purified by column chromatography silica-gel eluting with (n-Hexane:AcOEt=1:1) to give

cyclohexyl[1-[4-(2-hydroxyethoxy)phenyl]-2-(6-methoxy-3-pyridinyl)-1H-imidazol-4-yl]methanone (0.47 g).
1HNMR (200MHz, DMSOd6): 1.28 - 1.42 (5H, m), 1.66 - 1.85 (5H, m), 3.33 - 3.44 (1H, m), 3.69-3.77 (2H, m), 3.74 (2H, t, J = 4.8Hz), 3.84 (3H, s), 4.91 (1H, t, J = 5.3Hz), 6.82 (1H, d, J = 8.5Hz), 7.04 (2H, d, J = 8.5Hz), 7.33 (2H, d, J = 9Hz), 7.66 (1H, dd, J = 2.5 ,8.5Hz), 8.08 (1H, d, J = 2Hz), 8.19 (1H, s),
IR (KBr) : 3363, 3120, 2931, 2852, 1664, 1612 cm-1
Mass (ESI+) : 422 (M+H)+

Example 97

To a solution of 1-[1-[4-(2-hydroxyethoxy)phenyl]-2-(4-methoxyphenyl)-1H-imidazol-4-yl]-2-methyl-1-propanone (0.55 g) in dichloromethane (6 ml) was added methanesulfonyl chloride (123 μl) and triethylamine (222 μl) at 0℃. After stirring at room temperature for overnight, the mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated under reduced pressure to give 2-{4-[4-isobutyryl-2-(4-methoxyphenyl)-1H-imidazol-1-yl]phenoxy}ethyl methanesulfonate as an oil (0.66 g).
1HNMR (200MHz, DMSOd6): 1.14 (3H, s), 1.17 (3H, s), 3.02 - 3.09 (1H, m), 3.24 (3H, s), 3.76 (3H, s), 4.3 - 4.33 (2H, m), 4.53 - 4.55 (2H, m), 6.93 (2H, d, J = 9Hz), 7.09 (2H, d, J = 8.5Hz), 7.29 - 7.38 (4H, m), 7.36 (1H, s),
Mass (ESI+) : 458 (M+H)+

The following compound(s) was(were) obtained in a similar manner to that of Example 97.

Example 98

2-{4-[4-acetyl-2-(4-methoxyphenyl)-1H-imidazol-1-yl]-phenyl}ethyl methanesulfonate
1HNMR (200MHz, DMSOd6): 2.53 (3H, s), 3.04-3.11 (2H, m), 3.11 (3H, s), 3.77 (3H, s), 4.46 (2H, t, J = 6.5Hz), 6.93 (2H,

d, J = 9Hz), 7.29 - 7.48 (6H, m), 8.52 (1H, s),
IR (Neat) : 2962, 2927, 2848, 1707, 1691, 1676, 1658, 1647 cm-1
Mass (ESI+) : 415 (M+H)+

Example 99

A mixture of 2-{4-[4-isobutyryl-2-(4-methoxyphenyl)-1H-imidazol-1-yl]phenoxy}ethyl methanesulfonate (0.66 g) and potassium phthalimide (400 mg) in DMF (7 ml) was stirred at 60℃ for 3 hours. After cooling to room temperature, the reaction mixture was poured into water and extracted with ethyl acetate, dried over MgSO4 and evaporated in vacuo. to give 2-(2-{4-[4-isobutyryl-2-(4-methoxyphenyl)-1H-imidazol-1-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione (0.4 g).
1HNMR (200MHz, DMSOd6): 1.11 (3H, s), 1.15 (3H, s), 3.58 - 3.56 (1H, m), 3.73 (3H, s), 3.96 - 4.05 (2H, m), 4.24 - 4.29 (2H, m), 6.88 (2H, d, J = 9Hz), 6.99 (2H, d, J = 9Hz), 7.26 (4H, d, J = 9Hz), 7.83 - 7.93 (4H, m), 8.07 (1H, s),
Mass (ESI+) : 510 (M+H)+

The following compound(s) was(were) obtained in a similar manner to that of Example 99.

Example 100

2-(2-{4-[4-acetyl-2-(4-methoxyphenyl)-1H-imidazol-1-yl]phenyl}ethyl)-1H-isoindole-1,3(2H)-dione
1HNMR (200MHz, DMSOd6): 2.47 (3H, s), 3 (2H, t, J = 6.8Hz), 3.76 (3H, s), 3.87 (2H, t, J = 6.8Hz), 6.86 (2H, d, J = 9Hz), 7.19 - 7.34 (6H, m), 7.85 (4H, s), 8.13 (1H, s),
IR (Neat) : 3465, 3215, 3057, 3026, 2945, 2860, 1770, 1712, 1674, 1610 cm-1
Mass (ESI+) : 466 (M+H)+

Example 101

2-(2-{4-[4-isobutyryl-2-(4-methoxyphenyl)-1H-imidazol-1-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione (80 mg) and hydrazine hydride (23 ml) in acetonitrile (3 ml) was stirred

at reflux condition for 2 hours. After cooling at room temperature, The reaction mixture was poured into 1N aqueous sodium hydroxide and extracted with ethyl acetate, dried over MgSO4 and evaporated in vacuo. The residue was dissolved into dimethoxyethane (3 ml). Then sulfamide (45.3 mg) was added. After stirring at reflux condition for overnight, the mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative TLC to give N-(2-{4-[4-isobutyryl-2-(4-methoxyphenyl)-1H-imidazol-1-yl]phenoxy}ethyl)sulfamide (27.1 mg).

1HNMR (200MHz, DMSOd6): 1.12 (3H, s), 1.16 (3H, s), 3.2 - 3.31 (2H, m), 3.6 - 3.67 (1H, m), 3.74 (3H, s), 4.1 (2H, t, J = 5.8Hz), 6.39 (2H, b.s), 6.64 (1H, b.s), 6.9 (2H, d, J = 9Hz), 7.02 (2H, d, J = 9Hz), 7.26 - 7.32 (4H, m), 8.11 (1H, s),

IR (KBr) : 3325, 3215, 3130, 2968, 2935, 2873, 2839, 1662, 1610 cm-1

Mass (ESI+) : 459 (M+H)+

Example 102

NaH 60% in oil (43 mg) was added to a solution of 1-[1-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1H-imidazol-4-yl]ethanone (0.24 g) in DMF (3 ml). After stirring at room temperature for 30 minutes, t-Butyldimethylsilyloxy-ethylbromide (349 mg) was added. The mixture was stirred at room temperature for 4 hours. The reaction mixture was poured into water and extracted with ethyl acetate, dried over MgSO4 and evaporated in vacuo. The residue was purified by column chromatography silica-gel eluting with (n-Hexane:AcOEt=4:1) to give 1-[1-[4-(2-{[tert-butyl(dimethyl)silyl]oxy}ethoxy)-phenyl]-2-(4-methoxyphenyl)-1H-imidazol-4-yl]ethanone (0.24 g).

1HNMR (200MHz, DMSOd6): 0.07 (6H, s), 0.87 (9H, s), 3.74 (3H, s), 2.48 (3H, s), 3.93 (2H, t, J = 4.3Hz), 4.08 (2H, t, J = 4.3Hz), 6.88 (2H, d, J = 9Hz), 7.02 (2H, d, J = 9Hz),

7.28 (4H, d, J = 8.5Hz), 8.11 (1H, s),
IR (Neat) : 2949, 2935, 2891, 2858, 1676, 1612 cm-1
Mass (ESI+) : 467 (M+H)+

The following compound(s) was(were) obtained in a similar manner to that of Example 102.

Example 103
tert-butyl (2-{4-[4-acetyl-2-(4-methoxyphenyl)-1H-imidazol-1-yl]phenoxy}ethyl)carbamate
1HNMR (200MHz, DMSOd6): 1.39 (9H, s), 2.47 (3H, s), 3.29 - 3.34 (2H, m), 3.74 (3H, s), 3.97 - 4.08 (2H, m), 6.9 (2H, d, J = 10Hz), 7.00-7.04 (3H, m), 7.28 (4H, d, J = 8Hz), 8.12 (1H, s),
IR (Neat) : 3348, 3134, 3103, 3055, 2972, 2937, 2841, 1714, 1703, 1670, 1610 cm-1
Mass (ESI+) : 452 (M+H)+

Example 104
tBuOK (173 mg) was added to a solution of methyltriphenylphosphonium bromide (551 mg) in THF (1 ml). After stirring at room temperature for 10 minutes, 1-[1-[4-(2-{[tert-butyl(dimethyl)silyl]oxy}ethoxy)phenyl]-2-(4-methoxyphenyl)-1H-imidazol-4-yl]ethanone(0.24 g) in THF (2 ml) was added dropwise. After stirring at room temperature for 1 hour, the reaction mixture was poured into water and extracted with ethyl acetate, dried over MgSO4 and evaporated in vacuo. The residue was purified by column chromatography silica-gel eluting with (n-Hexane:AcOEt=4:1)to give 1-[4-(2-{[tert-butyl(dimethyl)silyl]oxy}ethoxy)phenyl]-4-isopropenyl-2-(4-methoxyphenyl)-1H-imidazole (0.24 g).
1HNMR (200MHz, DMSOd6): 0.07 (6H, s), 0.87 (9H, s), 2.02 (3H, s), 3.73 (3H, s), 3.92 (2H, t, J = 4.3Hz), 4.07 (2H, t, J = 4.5Hz), 4.87 - 4.89 (1H, m), 5.66 (1H, d, J = 3Hz), 6.85 (2H, d, J = 8.5Hz), 7.00 (2H, d, J = 8.5Hz), 7.20 - 7.28 (4H, m), 7.4 (1H, s),

IR (Neat) : 2951, 2933, 2893, 2858, 1641, 1612 cm-1
Mass (ESI+) : 465 (M+H)+

The following compound(s) was(were) obtained in a similar manner to that of Example 104.

Example 105

2-(2-{4-[4-isopropenyl-2-(4-methoxyphenyl)-1H-imidazol-1-yl]phenyl}ethyl)-1H-isoindole-1,3(2H)-dione
1HNMR (200MHz, DMSOd6): 2.01 (3H, s), 2.99 (2H, t, J = 7Hz), 3.75 (3H, s), 3.86 (2H, t, J = 7Hz), 4.87 - 4.89 (1H, m), 5.66 (1H, d, J = 2.5Hz), 6.83 (2H, d, J = 9Hz), 7.16 - 7.21 (4H, m), 7.29 (2H, d, J = 8Hz), 7.42 (1H, s), 7.63 (4H, s),
Mass (ESI+) : 464 (M+H)+

Example 106

tert-butyl (2-{4-[4-isopropenyl-2-(4-methoxyphenyl)-1H-imidazol-1-yl]phenoxy}ethyl)carbamate
1HNMR (200MHz, DMSOd6): 1.39 (9H, s), 2.02 (3H, s), 3.28 - 3.34 (2H, m), 3.73 (3H, s), 3.98 (2H, t, J = 5.8Hz), 4.84 - 4.89 (1H, m), 5.66 (1H, d, J = 2.5Hz), 6.87 (2H, d, J = 9Hz), 7 (2H, d, J = 9Hz), 7.03 - 7.07 (1H, m), 7.22 (2H, d, J = 7Hz), 7.26 (2H, d, J = 7.5Hz), 7.4 (1H, s),
IR (KBr) : 3359, 3134, 2968, 2933, 2844, 1714, 1701, 1610 cm-1
Mass (ESI+) : 450 (M+H)+

Example 107

1N tetrabutylammoniumfluoride in THF (1.03 ml) was added to a solution of 1-[4-(2-{[tert-butyl(dimethyl)silyl]oxy}ethoxy)-phenyl]-4-isopropenyl-2-(4-methoxyphenyl)-1H-imidazole (0.24 g) in THF (2 ml). After stirring at room temperature for 2 hours, the reaction mixture was poured into water and extracted with ethyl acetate, dried over MgSO4 and evaporated in vacuo. The residue was purified by column chromatography silica-gel eluting with (n-Hexane:AcOEt=1:1)to give

2-{4-[4-isopropenyl-2-(4-methoxyphenyl)-1H-imidazol-1-yl]phenoxy}ethanol (124 mg).
1HNMR (200MHz, DMSOd6): 2.02 (3H, s), 3.73 (3H, s), 3.71 - 3.76 (2H, m), 4.01 (2H, t, J = 5Hz), 4.87 - 4.91 (2H, m), 5.66 (1H, d, J = 2.6Hz), 6.87 (2H, d, J = 8.5Hz), 7 (2H, d, J = 9Hz), 7.2 - 7.28 (4H, m), 7.4 (1H, s),
IR (KBr) : 3118, 1670, 1612 cm-1
Mass (ESI+) : 351 (M+H)+

Example 108

2-(2-{4-[4-isopropenyl-2-(4-methoxyphenyl)-1H-imidazol-1-yl]phenyl}ethyl)-1H-isoindole-1,3(2H)-dione (1.07 g) and hydrazine hydride (1.12 ml) in acetonitrile (10 ml) was stirred at reflux condition for 2 hours. After cooling at room temperature, The reaction mixture was poured into 1N aqueous sodium hydroxide and extracted with ethyl acetate, dried over MgSO4 and evaporated in vacuo. to give 2-{4-[4-isopropenyl-2-(4-methoxyphenyl)-1H-imidazol-1-yl]phenyl}ethanamine (0.42 g).
1HNMR (200MHz, DMSOd6): 2.02 (3H, s), 2.68 - 2.82 (4H, m), 3.33 (2H, b.s), 3.74 (3H, s), 4.87 - 4.9 (1H, m), 5.66 (1H, d, J = 2.5Hz), 6.86 (2H, d, J = 9Hz), 7.17 - 7.31 (6H, m), 7.45 (1H, s),
IR (Neat) : 3367, 3288, 3130, 3039, 2937, 2843, 1699, 1685, 1637, 1612 cm-1
Mass (ESI+) : 334 (M+H)+

Example 109

To a solution of (2-{4-[4-isopropenyl-2-(4-methoxyphenyl)-1H-imidazol-1-yl]phenyl}ethyl)amine (0.14 g) in dichloromethane (3 ml) was added acetic anhydride (102 µl) and triethylamine (222 µl). After stirring at room temperature for 2 hours, the mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated under reduced pressure to give N-(2-{4-[4-isopropenyl-2-(4-methoxyphenyl)-1H-imidazol-1-yl]phenyl}ethyl)acetamide (0.12 g).

1HNMR (200MHz, DMSOd6): 2.02 (3H, s), 2.75 (2H, t, J = 7.3Hz), 3.26 (2H, t, J = 7.3Hz), 3.33 (3H, s), 3.74 (3H, s), 4.88 - 4.9 (1H, m), 5.66 (1H, d, J = 3Hz), 6.86 (2H, d, J = 9Hz), 7.187 - 7.32 (6H, m), 7.44 (1H, s), 7.94 (1H, t, J = 5.5Hz),
IR (KBr) : 3261, 3132, 3080, 2972, 2933, 2873, 2839, 1641, 1610 cm-1
Mass (ESI+) : 376 (M+H)+

The following compound(s) was(were) obtained in a similar manner to that of Example 109.

Example 110

N-(2-{4-[4-isopropenyl-2-(4-methoxyphenyl)-1H-imidazol-1-yl]phenoxy}ethyl)acetamide
1HNMR (200MHz, DMSOd6): 1.83 (3H, s), 2.02 (3H, s), 3.43 (2H, t, J = 5.5Hz), 3.73 (3H, s), 4.01 (2H, t, J = 5.5Hz), 4.87 - 4.9 (1H, m), 6.65 (1H, d, J = 2.5Hz), 6.86 (2H, d, J = 9Hz), 7.01 (2H, d, J = 9Hz), 7.22 (2H, d, J = 7Hz), 7.26 (2H, d, J = 6.5Hz), 7.4 (1H, s), 8.13 (1H, t, J = 5.3Hz),
IR (KBr) : 3234, 3128, 3066, 2937, 2875, 1628, 1612 cm-1
Mass (ESI+) : 392 (M+H)+

Example 111

4N HCl/AcOEt (4.62 ml) was added to as solution of tert-butyl (2-{4-[4-isopropenyl-2-(4-methoxyphenyl)-1H-imidazol-1-yl]phenoxy}ethyl)carbamate (0.83 g) in AcOEt (8 ml) at 0℃. After stirring at room temperature for 4 hours, resulting precipitates were collected by filtration to give (2-{4-[4-isopropenyl-2-(4-methoxyphenyl)-1H-imidazol-1-yl]phenoxy}ethyl)amine hydrochloride (0.66 g).
1HNMR (200MHz, DMSOd6): 2.11 (3H, s), 3.17 - 3.24 (2H, m), 3.8 (3H, s), 4.24 (2H, t, J = 5Hz), 5.35 (1H, s), 6.05 (1H, s), 7.04 (2H, d, J = 8.5Hz), 7.12 (2H, d, J = 9Hz), 7.44 - 7.49 (4H, m), 8.08 (1H, s), 8.38 (3H, b.s),
IR (KBr) : 3384, 3145, 3010, 2974, 2941, 2889, 2843, 1651, 1606 cm-1

Mass (ESI+) : 378 (M+H)+

Example 112

N-(2-{4-[4-isopropenyl-2-(4-methoxyphenyl)-1H-imidazol-1-yl]phenoxy}ethyl)acetamide (86 mg) and 10%Pd-C (20 mg) in EtOH (3 ml) was stirred at room temperature for 2 hours under H2. After filtration, the reaction mixture was evaporated in vacuo. to give N-(2-{4-[4-isopropyl-2-(4-methoxyphenyl)-1H-imidazol-1-yl]phenoxy}ethyl)acetamide (63 mg).

1HNMR (200MHz, DMSOd6): 1.24 (6H, d, J = 6.5Hz), 1.83 (3H, s), 2.77 - 2.9 (1H, m), 3.42 (2H, t, J = 5.5Hz), 3.73 (3H, s), 4 (2H, t, J = 5.5Hz), 6.84 (2H, d, J = 9Hz), 6.96 - 7.01 (3H, m), 7.16 - 7.24 (4H, m), 8.13 (1H, t, J = 5.5Hz),

IR (KBr) : 3257, 3134, 3087, 3055, 2964, 2941, 2871, 1674, 1610 cm-1

Mass (ESI+) : 394 (M+H)+

(continued to the next page)

Preparation 73

A mixture of 5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-1H-1,2,4-triazol-3-ol (1.5 g, 4.02 mmol), potassium carbonate (1.67 g, 12.1 mmol), and FR004230 (1.36 mL, 12.1 mmol) in dimethylformamide (15 mL) was stirred at 80 ℃ for 8 hours. 50 mL of water and 30 mL of ethyl acetate were poured into the reaction mixture and the aqueous solution was extracted with ethyl acetate for three times. The combine organic layer was washed with water and brine, and dried over magnesium sulfate. After filtration, the solvent was removed under reduced pressure. The residue was purified by column chromatography (toluene/ethyl acetate = 10/1) and eluent was evaporated in vacuo to give 5-[4-(benzyloxy)phenyl]-3-(2-ethoxyethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazole (1.0 g, 55.9%) as a pale brown powder.

1HNMR (200MHz, CDCl3): 1.23 (3H, t, J = 7Hz), 3.61 (2H, q, J = 7Hz), 3.8 - 3.84 (2H, m), 4.46 - 4.51 (2H, m), 5.05 (2H, s), 6.866 - 6.94 (4H, m), 7.245 - 7.46 (10H, m)

MS (ESI, m/e) 446 (M+1)

The following compound(s) was(were) obtained in a similar manner to that of Preparation 73.

Preparation 74

5-[5-[4-(benzyloxy)phenyl]-3-(2,2,2-trifluoroethoxy)-1H-1,2,4-triazol-1-yl]-2-methoxypyridine

1HNMR (200MHz, CDCl3): 3.98 (3H, s), 4.75 (2H, q, J = 8.2Hz), 5.02 (2H, s), 6.81 (1H, d, J = 8Hz), 6.93 (2H, d, J = 9Hz), 7.334 - 7.45 (7H, m), 7.57 (1H, dd, J = 2.8 ,8.5Hz), 8.16 (1H, d, J = 2Hz)

MS (ESI, m/e) 457 (M+1)

Preparation 75

5-[4-(benzyloxy)phenyl]-3-(cyclohexylmethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazole

1H NMR (DMSO-d6, ppm) d 0.91-1.40(5H, m), 1.51-1.90(11H, m),

3.80(3H, s), 4.04(2H, d, J=5.9 Hz), 5.10(2H, s), 7.01(4H, d, J=8.6 Hz), 7.25-7.55(9H, m),
MS (ESI, m/e) 470(M+1)

Preparation 76

2-{[5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-1H-1,2,4-triazol-3-yl]oxy}-1-phenylethanone
1H NMR (DMSO-d6, ppm) d 3.79(3H, s), 5.09(2H, s), 5.74(2H, s), 6.94-7.07(4H, m), 7.21-7.49(9H, m), 7.50-7.65(2H, m), 7.65-7.78(1H, m), 7.95-8.08(2H, m),
MS (ESI, m/e) 492(M+1)

Preparation 77

5-{5-[4-(benzyloxy)phenyl]-3-isopropoxy-1H-1,2,4-triazol-1-yl}-2-methoxypyridine
1H NMR (DMSO-d6, ppm) d 1.34(3H, s), 1.37(3H, s), 3.89(3H, s), 4.91(1H, 7th, J=6.2 Hz), 5.11(2H, s), 6.95(1H, d, J=8.9 Hz), 7.02-7.11(2H, m), 7.29-7.50(7H, m), 7.79(1H, dd, J=8.8,2.7 Hz), 8.21(1H, d, J=2.4 Hz),
MS (ESI, m/e) 417(M+1)

Preparation 78

5-[5-[4-(benzyloxy)phenyl]-3-(cyclopropylmethoxy)-1H-1,2,4-triazol-1-yl]-2-methoxypyridine
1H NMR (DMSO-d6, ppm) d 0.28-0.48(2H, m), 0.50-0.68(2H, m), 1.20-1.45(1H, m), 3.89(3H, s), 4.09(2H, d, J=7.2 Hz), 5.11(2H, s), 6.95(1H, d, J=8.9 Hz), 7.02-7.12(2H, m), 7.29-7.50(7H, m), 7.79(1H, dd, J=8.8,2.6 Hz), 8.21(1H, d, J=2.6 Hz),
MS (ESI, m/e) 429(M+1)

Preparation 79

5-{5-[4-(benzyloxy)phenyl]-3-isobutoxy-1H-1,2,4-triazol-1-yl}-2-methoxypyridine
1H NMR (DMSO-d6, ppm) d 0.98(6H, d, J=6.7 Hz), 1.92-2.19(1H, m), 3.89(3H, s), 4.03(2H, d, J=6.5 Hz), 5.11(2H, s), 6.95(1H, d, J=8.5 Hz), 7.00-7.10(2H, m), 7.27-7.50(7H, m), 7.79(1H, dd,

J=8.9,2.7 Hz), 8.21(1H, d, J=2.5 Hz),
MS (ESI, m/e) 431(M+1)

Preparation 80

5-[5-(4-bromophenyl)-3-(cyclopentyloxy)-1H-1,2,4-triazol-1-yl]-2-methoxypyridine
1H NMR (CDCl3, ppm) d1.52-2.10(8H, m), 3.97(3H, s), 5.18-5.30(1H, m), 6.81(1H, d, J=9.1 Hz), 7.30-7.41(2H, m), 7.42-7.51(2H, m), 7.57(1H, dd, J=8.7,2.7 Hz), 8.13(1H, d, J=2.4 Hz),
MS (ESI, m/e) 416(M+1)

Preparation 81

A mixture of 5-[4-(benzyloxy)phenyl]-3-(2-ethoxyethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazole (976 mg, 2.19 mmol) and Pd-C (50% wet, 208 mg) in ethanol-THF solution (8 ml + 4 ml) was stirred under hydrogen gas atmosphere at room temperature for 1.5 hours. After filtration, the reaction mixture was evaporated in vacuo to give 4-[3-(2-ethoxyethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenol (770 mg, 98.9%) as a colorless powder.
1HNMR (200MHz, DMSOd6): 1.13 (3H, t, J = 7 Hz), 3.5 (3H, q, J = 7 Hz), 3.678 - 3.72 (2H, m), 3.8 (3H, s), 4.311 - 4.36 (2H, m), 6.73 (2H, d, J = 8.5 Hz), 7.02 (2H, d, J = 9 Hz), 7.22 (2H, d, J = 8.5 Hz), 7.29 (2H, d, J = 9 Hz)
MS (ESI, m/e) 356 (M+1)

The following compound(s) was(were) obtained in a similar manner to that of Preparation 81.

Preparation 82

4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenol
1HNMR (200MHz, CDCl3): 3.99 (3H, s), 6.28 (1H, s), 6.79 (2H, d, J = 9Hz), 6.86 (1H, d, J = 9.5Hz), 7.38 (2H, d, J = 8.5Hz), 7.64 (1H, dd, J = 2.6 ,8.6Hz), 8.17 (1H, d, J = 2.5Hz)
MS (ESI, m/e) 337 (M+1)

Preparation 83

4-[1-(6-methoxy-3-pyridinyl)-3-(2,2,2-trifluoroethoxy)-1H-1,2,4-triazol-5-yl]phenol

1HNMR (200MHz, CDCl3): 3.98 (3H, s), 4.74 (2H, q, J = 8.2Hz), 6.57 (1H, s), 6.76 (2H, d, J = 8.5Hz), 6.82 (1H, d, J = 9.5Hz), 7.33 (2H, d, J = 8.5Hz), 7.6 (1H, dd, J = 2.8 ,8.5Hz), 8.12 (1H, d, J = 2.5Hz)

MS (ESI, m/e) 367 (M+1)

Preparation 84

4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenol

1HNMR (200MHz, DMSOd6): 3.83 (3H, s), 6.77 (2H, d, J = 8.5Hz), 7.08 (2H, d, J = 9Hz), 7.31 (2H, d, J = 8.5Hz), 7.45 (2H, d, J = 9Hz), 10.11 (1H, b.s)

MS (ESI, m/e) 358 (M+Na)

Preparation 85

4-[1-(4-methoxyphenyl)-3-(1-piperidinylcarbonyl)-1H-1,2,4-triazol-5-yl]phenol

1HNMR (200MHz, CDCl3): 1.68 (6H, b.s), 3.79 (4H, b.s), 3.84 (3H, s), 6.76 (2H, d, J = 9Hz), 6.9 (2H, d, J = 9Hz), 7.24 (4H, d, J = 9.5Hz)

MS (ESI, m/e) 379 (M+1)

Preparation 86

5-(4-hydroxyphenyl)-N-methoxy-1-(6-methoxy-3-pyridinyl)-N-methyl-1H-1,2,4-triazole-3-carboxamide

1HNMR (200MHz, CDCl3): 3.49 (3H, b.s), 3.9 (3H, s), 3.98 (3H, s), 6.81 (2H, d, J = 9Hz), 6.82 (1H, d, J = 9Hz), 7.34 (2H, d, J = 8.5Hz), 7.61 (1H, dd, J = 2.5 ,9Hz), 8.18 (1H, d, J = 2.5Hz)

MS (ESI, m/e) 356 (M+1)

Preparation 87

1-[5-(4-hydroxyphenyl)-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-3-yl]-2-methyl-1-propanone
1HNMR (200MHz, DMSOd6): 1.18 (6H, d, J = 6.5Hz), 3.68 (1H, sept, J = 7Hz), 3.92 (3H, s), 6.79 (2H, d, J = 8.5Hz), 7 (1H, d, J = 8.5Hz), 7.33 (2H, d, J = 9Hz), 7.88 (1H, dd, J = 2.8 ,8.5Hz), 8.32 (1H, d, J = 2Hz)
MS (ESI, m/e) 339 (M+1)

Preparation 88

4-[3-(cyclopentylmethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenol
1H NMR (DMSO-d6, ppm) d 1.21-1.44(2H, m), 1.45-1.68(4H, m), 1.68-1.89(2H, m), 2.34(1H, 7th, J=7.4 Hz), 3.80(3H, s), 4.10(2H, d, J=7.1 Hz), 6.68-6.80(2H, m), 6.95-7.08(2H, m), 7.15-7.36(4H, m), 9.97(1H, bs),
MS (ESI, m/e) 366(M+1)

Preparation 89

4-[3-(cyclohexylmethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenol
1H NMR (DMSO-d6, ppm) d 0.91-1.42(5H, m), 1.55-1.90(6H, m), 3.80(3H, s), 4.04(2H, d, J=5.9 Hz), 6.65-6.79(2H, m), 6.95-7.09(2H, m), 7.15-7.38(4H, m), 9.96(1H, s),
MS (ESI, m/e) 380(M+1)

Preparation 90

4-[3-isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenol
1H NMR (DMSO-d6, ppm) d 1.33(3H, s), 1.36(3H, s), 3.89(3H, s), 4.90(1H, 7th, J=6.2 Hz), 6.71-6.86(2H, m), 6.94(1H, d, J=8.9 Hz), 7.19-7.35(2H, m), 7.76(1H, dd, J=8.8,2.8 Hz), 8.19(1H, d, J=2.8 Hz), 10.02(1H, bs),
MS (ESI, m/e) 327(M+1)

Preparation 91

4-[3-(cyclopropylmethoxy)-1-(6-methoxy-3-pyridinyl)-1H-

1,2,4-triazol-5-yl]phenol
1H NMR (DMSO-d6, ppm) d 0.28-0.43(2H, m), 0.52-0.66(2H, m), 1.19-1.40(1H, m), 3.89(3H, s), 4.08(2H, d, J=7.2 Hz), 6.70-6.86(2H, m), 6.94(1H, d, J=8.6 Hz), 7.76(1H, dd, J=8.8,2.8 Hz), 8.18(1H, d, J=2.6 Hz), 10.02(1H, bs),
MS (ESI, m/e) 339(M+1)

Preparation 92

4-[3-isobutoxy-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenol
1H NMR (DMSO-d6, ppm) d 0.98(6H, d, J=6.7 Hz), 1.93-21.19(1H, m), 3.89(3H, s), 4.02(2H, d, J=6.5 Hz), 6.67-6.82(2H, m), 6.94(2H, d, J=8.6 Hz), 7.19-7.35(2H, m), 7.77(1H, dd, J=8.9,2.7 Hz), 8.19(1H, d, J=2.5 Hz), 10.0(1H, bs),
MS (ESI, m/e) 341(M+1)

Preparation 93

To a conc. HCl solution of 6-methoxy-3-pyridinamine (52.04 g, 419 mmol) was added an aqueous solution of NaNO2 over a 10 min period and stirred at this temperature for 15 min. To this reaction mixture was added a solution of tindichloride in hydrogenchloride over a 60 min period. After filtration, the resulting pale red solid was washed with ether, methanol, and ether, and dried to give 5-hydrazino-2-methoxypyridine dihydrochloride (78 g, 87.7%) as a pale brown powder.
1HNMR (200MHz, DMSOd6): 3.81 (3H, s), 6.83 (1H, d, J = 9Hz), 7.55 (1H, dd, J = 3 ,9Hz), 7.96 (1H, d, J = 2.5Hz), 10.29 (3H, b.s)

Preparation 94

To an aqueous solution of 5-hydrazino-2-methoxypyridine dihydrochloride (180.5 g, 851 mmol) was added a potassium cyanate (138 g, 1.7 mol). This mixture was stirred for 1 hour and the resulting brown solid was filtrated. The filtrates was washed with ethyl acetate and dried to give 2-(6-methoxy-3-pyridinyl)hydrazinecarboxamide (124 g, 80%) as

a brown solid.
MS (ESI, m/e) 205 (M+Na)

Preparation 95

To a suspention of the 2-(6-methoxy-3-pyridinyl)hydrazinecarboxamide (60 g, 329 mmol) in dichloromethan (600 ml) were added pyridien (29.3 ml, 362 mmol) and FR046879 (89.4 g, 362 mmol) at 0 ℃ and stirred for 3 hours. The resulting presipitate was filtrated and washed with dichloromethane, water, and toluene. The filtrates was dried to give 2-[4-(benzyloxy)benzoyl]-2-(6-methoxy-3-pyridinyl)hydrazinecarboxamide (94 g, 72.7%) as a pale brown solid.
1HNMR (200MHz, DMSOd6): 3.83 (3H, s), 5.14 (2H, s), 6.84 (1H, d, J = 8.5Hz), 7.02 (2H, d, J = 9Hz), 7.331 - 7.56 (9H, m), 7.73 (1H, d, J = 8.5Hz), 8.15 (1H, b.s), 8.97 (1H, b.s)

The following compound(s) was(were) obtained in a similar manner to that of Preparation 95.

Preparation 96

2-(4-bromobenzoyl)-2-(6-methoxy-3-pyridinyl)hydrazine-carboxamide
1HNMR (200MHz, DMSOd6): 3.84 (3H, s), 6.86 (1H, d, J = 9Hz), 7.526 - 8.22 (6H, m)

Preparation 97

To an ethanol solution (300 ml) of 2-[4-(benzyloxy)benzoyl]-2-(6-methoxy-3-pyridinyl)hydrazinecarboxamide (94 g, 240 mmol) was added an aqueous solution of sodium hydroxide (10%, 300 ml) and stirred at 60 ℃ for 4 hours. After filtration, the filtrate was neutralized by 2N HCl (aq.). The resulting precipitate was filtrated and washed with water and ethyl acetate to give 5-[4-(benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-3-ol (76.9 g, 85.7%) as a pale brown solid.

1HNMR (200MHz, DMSOd6): 3.89 (3H, s), 5.11 (2H, s), 6.93 (1H, d, J = 8.5Hz), 7.02 (2H, s), 7.339 - 7.46 (7H, m), 7.75 (1H, dd, J = 2.8 ,9Hz), 8.19 (1H, d, J = 2.5Hz)

The following compound(s) was(were) obtained in a similar manner to that of Preparation 97.

Preparation 98

5-(4-bromophenyl)-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-3-ol

1HNMR (200MHz, DMSOd6): 3.89 (3H, s), 6.94 (1H, d, J = 8Hz), 7.36 (2H, d, J = 8.5Hz), 7.612 - 7.79 (3H, m), 8.2 (1H, d, J = 2Hz)

MS (ESI, m/e) 370 (M+Na)

Preparation 99

To a suspention of 5-hydrazino-2-methoxypyridine dihydrochloride (5.68 g, 26.8 mmol) and 2,2,2-trifluoroethanimidamide (4.5 g, 40.2 mmol) in methanol was added triethylamine (7.47 ml, 53.6 mmol) and stirred at room temperature for 15 hours. The reaction mixture was concentrated and residual oil was poured into 100 mL of water and 100 mL of ethyl acetate. The aqueous layer was extracted with ethyl acetate and the organic layer was washed with water and brine. This solution was dried over magnesium sulfate and filtered. After removal of the solvent under reduced pressure, the residual oil containing (1E)-2,2,2-trifluoro-N'-(6-methoxy-3-pyridinyl)ethane-hydrazonamide was used for the next reaction without further purification.

The following compound(s) was(were) obtained in a similar manner to that of Preparation 99.

Preparation 100

(1E)-2,2,2-trifluoro-N'-(4-methoxyphenyl)ethane-hydrazonamide

Preparation 101

To a solution of (1E)-2,2,2-trifluoro-N'-(6-methoxy-3-pyridinyl)ethanehydrazonamide (6.3 g, 26.9 mmol) in 80 ml of dioxane were added pyridine (2.18 ml, 26.9 mmol) and a solution of 4-(benzyloxy)benzoyl chloride (6.64 g, 26.9 mmol) in 20 ml of dioxane. The mixture was refluxed for 4 hours and the solvent was removed under reduced pressure. 40 mL of ethyl acetate and 40 mL of 0.1 N HCl solution were added to the residue and the organic layer was separated. The aqueous layer was extracted with ethyl acetate and the combine organic layer was washed with water and brine. This solution was dried over magnesium sulfate and filtered. After removal of the solvent under reduced pressure, the residual oil was placed on a column of silica and eluted with hexsan/ethyl acetate (4/1). The eluent was evaporated and dried over in vacuo to give 5-[5-[4-(benzyloxy)phenyl]-3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl]-2-methoxypyridine (4.27 g, 37.2%) as a pale brown solid.

1HNMR (200MHz, CDCl3): 3.99 (3H, s), 5.08 (2H, s), 6.84 (1H, d, J = 9Hz), 6.96 (2H, d, J = 9Hz), 7.357 - 7.44 (5H, m), 7.47 (2H, d, J = 9Hz), 7.61 (1H, dd, J = 2.8 ,8.5Hz), 8.2 (1H, d, J = 2.5Hz)

MS (ESI, m/e) 427 (M+1)

The following compound(s) was(were) obtained in a similar manner to that of Preparation 101.

Preparation 102

5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-1,2,4-triazole

1HNMR (200MHz, DMSOd6): 3.83 (3H, s), 5.12 (2H, s), 7.041 - 7.11 (4H, m), 7.327 - 7.49 (9H, m)

MS (ESI, m/e) 426 (M+1)

Preparation 103

A suspention of diethyl aminomalonate hydrochloride (20 g, 94.5

mmol) in CH2Cl2 (200 ml) was cooled to 0 ℃ and to the mixture was added triethylamine (39.5 ml, 284 mmol) followed by 4-(benzyloxy)benzoyl chloride (24.5 g, 99.2 mmol). The reaction mixture was stirred at 0 ℃ for 3 hours. Dichloromethan was removed under reduced pressure and 100 ml of water and 100 ml of ethyl acetate was poured into the reaction mixture and the aqueous solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over magnesium sulfate. After filtration, the solvent was removed under reduced pressure. To the residual solid was purified by recrystalization from IPE to give diethyl {[4-(benzyloxy)benzoyl]amino}malonate (33.3 g, 91.4%) as a colorless crystal.

1HNMR (200MHz, CDCl3): 1.32 (3H, t, J = 7Hz), 4.248 - 4.37 (2H, m), 5.12 (2H, s), 5.33 (1H, d, J = 7Hz), 6.995 - 7.04 (3H, m), 7.331 - 7.45 (5H, m), 7.81 (2H, d, J = 9Hz)

MS (ESI, m/e) 386 (M+1)

Preparation 104

A solution of 4-methoxyaniline (1.53g, 12.5 mmol) in AcOH (8 ml) and conc. HCl (1.5 ml) was cooled to -5 ℃ under ice-salt bath. The aqueous solution (4 ml) of NaNO2 (859 mg, 12.5 mmol) was added to this mixture over a 15 min period and the reaction mixture was stirred at the same temperature for 15 min. Then, an acetone solution of diethyl {[4-(benzyloxy)benzoyl]amino}malonate (4g, 10.4 mmol) was added to the mixture. After 15 min, an aqueous solution of K2CO3 (14.3 g, 104 mmol) was added to the mixture over a 30 min period and the mixture was stirred for 3 hours at the same temperature. The reaction mixture was poured 50 ml of ethyl acetate and the aqueous layer was extracted with ethyl acetate. The combine organic layer was washed with sat. NaHCO3 aq., and brine and dried over magnesium sulfate. After filtration, the resulting oil was dissolved to ethanol. To this solution was added a sodium ethoxide and the mixture was stirred at 60 ℃ for 8 hours. After removal of the solvent under reduced pressure, the residual oil

was placed on a column of silica and eluted with ethyl acetate/hexsan (1/3 => 1/2). The eluent was evaporated and the resulting solid was purified by the recrystalization from ethyl acetate-hexsan to give ethyl 5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-1H-1,2,4-triazole-3-carboxylate (2.74 g, 61.5%) as a pale yellow solid.

1HNMR (200MHz, CDCl3): 1.45 (3H, t, J = 7Hz), 3.86 (3H, s), 4.53 (2H, q, J = 7.2Hz), 5.06 (2H, s), 6.894 - 6.96 (4H, m), 7.263 - 7.42 (7H, m), 7.5 (2H, d, J = 9Hz)

MS (ESI, m/e) 430 (M+1)

The following compound(s) was(were) obtained in a similar manner to that of Preparation 104.

Preparation 105

ethyl 5-[4-(benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazole-3-carboxylate

1HNMR (200MHz, CDCl3): 1.46 (3H, t, J = 7.3Hz), 3.98 (3H, s), 4.54 (2H, q, J = 7.2Hz), 5.08 (2H, s), 6.82 (1H, d, J = 8Hz), 6.95 (2H, d, J = 9Hz), 7.33 - 7.42 (5H, m), 7.49 (2H, d, J = 9Hz), 7.62 (1H, dd, J = 2.8 ,8.5Hz), 8.2 (1H, d, J = 2Hz)

MS (ESI, m/e) 431 (M+1)

Preparation 106

A suspention of ethyl 5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-1H-1,2,4-triazole-3-carboxylate (1.02 g, 2.38 mmol) in piperidine (5 ml) was heated at 80 ℃ for 15 hours. 50 mL of water and 50 mL of ethyl acetate were poured into the reaction mixture and the aqueous solution was extracted with ethyl acetate. The combine organic layer was washed with 1N HCl aq., water, and brine, and dried over magnesium sulfate. After filtration, the solvent was removed under reduced pressure. The residual solid was purified by column chromatography (ethyl acetate/hexsan = 1/1) and eluent was evaporated. The residue was recrystalized from ethyl acetate-hexsan to give

1-{[5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-1H-1,2,4-triazol-3-yl]carbonyl}piperidine (850 mg, 76.4%) as a colorless crystal.

1HNMR (200MHz, CDCl3): 1.69 (6H, b.s), 3.77 (4H, b.s), 3.86 (3H, s), 5.07 (2H, s), 6.897 - 6.96 (4H, m), 7.286 - 7.5 (9H, m)

MS (ESI, m/e) 469 (M+1)

Preparation 107

To a suspension of N,O-dimethylhydroxylamine hydrochloride (3.41 g, 34.9 mmol) was added a hexsan solution of AlMe3 at 0 ℃ under nitrogen atmosphere and stirred at room temperature for 1 hour. To this reaction mixture was added a THF solution of ethyl 5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-1H-1,2,4-triazole-3-carboxylate (5.0 g, 11.6 mmol) and refluxed for 5 hours. The reaction mixture was quented by a 1N HCl and THF was removed under reduced pressure. The aqueous layer was extracted with ethyl acetate and the organic rayer was washed with water, and brine. The solution was dried over magnesium sulfate and filtrated. After removal of the solvent under reduced pressure, the residual oil was placed on a column of silica and eluted with ethyl acetate/hexsan (1/1 => 2/1). The eluent was evaporated to give 5-[4-(benzyloxy)phenyl]-N-methoxy-1-(4-methoxyphenyl)-N-methyl-1H-1,2,4-triazole-3-carboxamide (3.25 g, 62.8%) as a pale yellow oil.

1HNMR (200MHz, CDCl3): 3.49 (3H, b.s), 3.86 (3H, s), 3.9 (3H, s), 5.06 (2H, s), 6.898 - 6.96 (4H, m), 7.289 - 7.5 (9H, m)

MS (ESI, m/e) 445 (M+1)

The following compound(s) was(were) obtained in a similar manner to that of Preparation 107.

Preparation 108

5-[4-(benzyloxy)phenyl]-N-methoxy-1-(6-methoxy-3-pyridinyl)-N-methyl-1H-1,2,4-triazole-3-carboxamide

1HNMR (200MHz, CDCl3): 3.48 (3H, b.s), 3.91 (3H, s), 3.99

(3H, s), 5.08 (2H, s), 6.82 (1H, d, J = 8Hz), 6.95 (2H, d, J = 9Hz), 7.357 - 7.51 (7H, m), 7.61 (1H, dd, J = 2.8 ,8.5Hz), 8.22 (1H, d, J = 2.5Hz)
MS (ESI, m/e) 446 (M+1)

Preparation 109

A solution of [5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-1H-1,2,4-triazol-3-yl](phenyl)methanone (1.0g, 2.17 mmol) in trifluoroacetic acid (5 ml) was cooled to 0℃. Thioanisole (1.02 ml, 8.67 mmol) was added to this mixture and stirred at room temperature for 20 hours. The reaction mixture was poured to a ice-water (30 ml) and neutralized by 1N NaOH aq. The aqueous solution was extracted with ethyl acetate and the organic layer was washed with water and brine. This solution was dried over magnesium sulfate and filtered. After removal of the solvent under reduced pressure, the residual oil was crystalized by the addition of IPE. The resulting solid was filtrated and washed with IPE to give [5-(4-hydroxyphenyl)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-3-yl](phenyl)methanone (752 mg, 93.4%) as a pale yellow solid.
1HNMR (200MHz, CDCl3): 3.86 (3H, s), 6.79 (2H, d, J = 8.5Hz), 6.96 (2H, d, J = 9Hz), 7.329 - 7.62 (7H, m), 8.405 - 8.45 (2H, m)
MS (ESI, m/e) 372 (M+1)

The following compound(s) was(were) obtained in a similar manner to that of Preparation 109.

Preparation 110

1-[5-(4-hydroxyphenyl)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-3-yl]-2-methyl-1-propanone
1HNMR (200MHz, DMSOd6): 1.18 (6H, d, J = 7Hz), 3.68 (1H, sept, J = 7Hz), 3.83 (3H, s), 6.77 (2H, d, J = 8.5Hz), 7.07 (2H, d, J = 9Hz), 7.3 (2H, d, J = 8.5Hz), 7.41 (2H, d, J = 9Hz), 10.05 (1H, b.s)

MS (ESI, m/e) 338 (M+1)

Preparation 111

2-{[5-(4-hydroxyphenyl)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-3-yl]oxy}-1-phenylethanone

1H NMR (DMSO-d6, ppm) d 3.79(3H, s), 5.73(2H, s), 6.65-6.79(2H, m), 6.95-7.08(2H, m), 7.13-7.36(4H, m), 7.50-7.78(3H, m), 7.92-8.08(2H, m), 9.97(1H, bs),

MS (ESI, m/e) 402(M+1)

Preparation 112

To a suspention of 5-[4-(benzyloxy)phenyl]-N-methoxy-1-(4-methoxyphenyl)-N-methyl-1H-1,2,4-triazole-3-carboxamide (1.0 g, 2.25 mmol) in ether (10 ml) was added a THF solution of isopropylmagnesiumbromide (5.92 ml, 4.5 mmol) at -78 ℃ under nitrogen atmosphere. The reaction mixture was warmed to room temperature and stirred for 3 hours. To this mixture was added an aqueous solution of NH4Cl and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with water and brine and dried over magnesium sulfate. After filtration, the solvent was removed under reduced pressure and the residual oil was crystalized by the addition of IPE. The resulting solid was filtrated and washed with IPE to give 1-[5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-1H-1,2,4-triazol-3-yl]-2-methyl-1-propanone (889 mg, 92.4%) as a pale yellow solid.

1HNMR (200MHz, CDCl3): 1.29 (6H, d, J = 7Hz), 3.79 (1H, sept, J = 7Hz), 3.87 (3H, s), 5.07 (2H, s), 6.92 (2H, d, J = 8.5Hz), 6.96 (2H, d, J = 9Hz), 7.261 - 7.52 (9H, m)

MS (ESI, m/e) 428 (M+1)

The following compound(s) was(were) obtained in a similar manner to that of Preparation 112.

Preparation 113

[5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-1H-1,2,4-

triazol-3-yl](phenyl)methanone
1HNMR (200MHz, CDCl3): 3.87 (3H, s), 5.08 (2H, s), 6.92 - 6.99 (4H, m), 7.339 - 7.61 (12H, m), 8.407 - 8.45 (2H, m)
MS (ESI, m/e) 462 (M+1)

Preparation 114
[5-[4-(2-hydroxyethoxy)phenyl]-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-3-yl](phenyl)methanone
1HNMR (200MHz, CDCl3): 2.02 (1H, t, J = 6Hz), 3.949 - 4.02 (5H, m), 4.097 - 4.14 (2H, m), 6.85 (1H, d, J = 8Hz), 6.93 (2H, d, J = 8.5Hz), 7.473 - 7.68 (7H, m), 8.27 (1H, d, J = 2Hz), 8.43 (1H, dd, J = 1.8 ,8.5Hz)
MS (ESI, m/e) 417 (M+1)

Preparation 115
1-[5-[4-(2-hydroxyethoxy)phenyl]-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-3-yl]-2-methyl-1-propanone
1HNMR (200MHz, CDCl3): 1.3 (6H, d, J = 7Hz), 1.98 (1H, sept, J = 6.3Hz), 3.78 (1H, t, J = 7Hz), 3.943 - 4.02 (2H, m), 3.99 (3H, s), 4.086 - 4.13 (2H, m), 6.83 (1H, d, J = 8.5Hz), 6.91 (2H, d, J = 8.5Hz), 7.5 (2H, d, J = 9Hz), 7.61 (1H, dd, J = 2.8 ,9Hz), 8.21 (1H, d, J = 2.5Hz)
MS (ESI, m/e) 383 (M+1)

Preparation 116
N-(2-{4-[3-benzoyl-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea
1HNMR (200MHz, CDCl3): 3.61 (2H, q, J = 5.4Hz), 4 (3H, s), 4.05 (2H, t, J = 5.3Hz), 4.43 (2H, b.s), 5.05 (1H, b.s), 6.84 (1H, d, J = 9Hz), 6.88 (2H, d, J = 8.5Hz), 7.482 - 7.67 (7H, m), 8.25 (1H, d, J = 2.5Hz), 8.397 - 8.44 (2H, m)
MS (ESI, m/e) 459 (M+1)

Preparation 117
N-(2-{4-[3-benzoyl-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)methanesulfonamide

1HNMR (200MHz, CDCl3): 3.03 (3H, s), 3.57 (2H, q, J = 5.5Hz), 4 (3H, s), 4.14 (2H, t, J = 5Hz), 4.83 (1H, b.s), 6.85 (1H, d, J = 9Hz), 6.89 (2H, d, J = 9Hz), 7.481 - 7.68 (7H, m), 8.26 (1H, d, J = 2.5Hz), 8.399 - 8.44 (1H, m)

MS (ESI, m/e) 494 (M+1)

Preparation 118

N-(2-{4-[3-isobutyryl-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)methanesulfonamide

1HNMR (200MHz, DMSOd6): 1.19 (6H, d, J = 6.5Hz), 2.94 (3H, s), 3.318 - 3.41 (2H, m), 3.69 (1H, sept, J = 7Hz), 3.92 (3H, s), 4.06 (2H, t, J = 5.5Hz), 6.985 - 7.04 (3H, m), 7.45 (2H, d, J = 8.5Hz), 7.89 (1H, dd, J = 2.8 ,9Hz), 8.34 (1H, d, J = 2.5Hz)

MS (ESI, m/e) 460 (M+1)

Preparation 119

1-[5-[4-(benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-3-yl]-2-methyl-1-propanone

1HNMR (200MHz, CDCl3): 1.3 (6H, d, J = 7Hz), 3.78 (1H, t, J = 6.8Hz), 3.99 (3H, s), 5.08 (2H, s), 6.83 (1H, d, J = 9Hz), 6.96 (2H, d, J = 8.5Hz), 7.337 - 7.42 (5H, m), 7.49 (2H, d, J = 9Hz), 7.61 (1H, dd, J = 2.8 ,9Hz), 8.22 (1H, d, J = 2.5Hz)

MS (ESI, m/e) 429 (M+1)

Preparation 120

Under ice-bath cooling, diethyl azodicarboxylate (DEAD, 909 mg, 5.22 mmol) was added to a suspension of 5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-1H-1,2,4-triazol-3-ol (1.5 g, 4.02 mmol) and triphenylphosphine (1.37 g, 5.22 mmol) in 15 ml of THF under nitrogen atmosphere. The mixture was stirred for 7 hours at room temperature. The solvent was removed under reduced pressure. The residue was purified by silicagel column chromatography to give 5-[4-(benzyloxy)phenyl]-3-(cyclopentylmethoxy)-1-(4-

methoxyphenyl)-1H-1,2,4-triazole (1.1 g, 60% yield).
1H NMR (DMSO-d6, ppm) d 1.20-1.45(2H, m), 1.46-1.67(4H, m), 1.67-1.88(2H, m), 2.34(1H, 7th, J=7.3 Hz), 3.80(3H, s), 4.11(2H, d, J=7.1 Hz), 5.10(2H, s), 6.92-7.08(4H, m), 7.24-7.50(9H, m),
MS (ESI, m/e) 456(M+1)

Preparation 121

Under nitrogen atmosphere, 5-[5-(4-bromophenyl)-3-(cyclopentyloxy)-1H-1,2,4-triazol-1-yl]-2-methoxypyridine (1.1 g, 2.65 mmol), zinc cyanide (311 mg, 2.65 mmol) and tetrakis(triphenylphosphine)palladium(0) (153 mmg, 0.13 mmol) were dissolved in DMF (10 ml). The solution was stirred for 16hr at 85C. After cooling, ethyl acetate and water were poured into the mixture and an insoluble material was removed by filtration. The organic layer was separated, washed with water and brine and dried over magnesium sulfate. The solvent was removed under reduced pressure. The residue was purified by silicagel chromatography (Hexane:Ethyl acetate 4:1). The desired product 4-[3-(cyclopentyloxy)-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]benzonitrile was isolated by filtration ,washed with isopropylether and dried in vacuo. (860 mg, 90% yield)
1H NMR (CDCl3, ppm) d 1.57-2.08(8H, m), 3.89(3H, s), 5.17-5.31(1H, m), 6.84(1H, d, J=8.5 Hz), 7.55-7.71(5H, m), 8.11(1H, d, J=2.9 Hz),
MS (ESI, m/e) 362(M+1)

Example 113

A mixture of 4-[3-(2-ethoxyethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenol (700 mg, 1.97 mmol), potassium carbonate (1.63 g, 11.8 mmol), potassium Iodide (981 mg, 5.91 mmol), and FR006638 (0.79 mL, 11.8 mmol) in dimethylformamide (7 mL) was stirred at 75 ℃ for 15 hours. 50 mL of water and 40 mL of ethyl acetate were poured into the reaction mixture and the aqueous solution was extracted with ethyl acetate for three times. The combine organic layer was washed with water and brine, and dried over magnesium sulfate. After filtration, the solvent

was removed under reduced pressure. The residue was purified by column chromatography (hexsan/ethyl acetate 1/1 => 1/2) and eluent was evaporated in vacuo to give 2-{4-[3-(2-ethoxyethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethanol (638 mg, 81.1%) as a colorless solid.

1HNMR (200MHz, CDCl3): 1.23 (3H, t, J = 7Hz), 3.61 (2H, q, J = 7Hz), 3.802 - 3.84 (2H, m), 3.84 (3H, s), 3.92 - 3.99 (2H, m), 4.055 - 4.1 (2H, m), 4.462 - 4.51 (2H, m), 6.83 (4H, d, J = 8.5Hz), 6.91 (2H, d, J = 9Hz), 7.26 (2H, d, J = 9Hz), 7.42 (2H, d, J = 8.5Hz)

MS (ESI, m/e) 400 (M+1)

The following compound(s) was(were) obtained in a similar manner to that of Example 113.

Example 114

2-{4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethanol

1HNMR (200MHz, CDCl3): 3.944 - 4.02 (2H, m), 3.99 (3H, s), 4.089 - 4.13 (2H, m), 6.85 (1H, d, J = 8Hz), 6.92 (2H, d, J = 9Hz), 7.48 (2H, d, J = 9Hz), 7.61 (1H, dd, J = 2.8 ,9Hz), 8.2 (1H, d, J = 2.5Hz)

MS (ESI, m/e) 381 (M+1)

Example 115

2-{4-[1-(4-methoxyphenyl)-3-(1-piperidinylcarbonyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethanol

1HNMR (200MHz, CDCl3): 1.69 (6H, b.s), 2.1 (1H, t, J = 6Hz), 3.77 (4H, b.s), 3.86 (3H, s), 3.929 - 4 (2H, m), 4.069 - 4.11 (2H, m), 6.86 (2H, d, J = 9Hz), 6.94 (2H, d, J = 9Hz), 7.3 (2H, d, J = 9Hz), 7.47 (2H, d, J = 9Hz)

MS (ESI, m/e) 423 (M+1)

Example 116

[5-[4-(2-hydroxyethoxy)phenyl]-1-(4-methoxyphenyl)-1H-

1,2,4-triazol-3-yl](phenyl)methanone
1HNMR (200MHz, CDCl3): 2.07 (1H, t, J = 6Hz), 3.87 (3H, s), 3.94 - 4.01 (2H, m), 4.083 - 4.13 (2H, m), 6.89 (2H, d, J = 9Hz), 6.97 (2H, d, J = 9Hz), 7.36 (2H, d, J = 9Hz), 7.464 - 7.62 (5H, m), 8.404 - 8.45 (2H, m)
MS (ESI, m/e) 416 (M+1)

Example 117
5-[4-(2-hydroxyethoxy)phenyl]-N-methoxy-1-(6-methoxy-3-pyridinyl)-N-methyl-1H-1,2,4-triazole-3-carboxamide
1HNMR (200MHz, CDCl3): 3.48 (3H, b.s), 3.91 (3H, s), 3.985 - 4.01 (5H, m), 4.085 - 4.13 (2H, m), 6.82 (1H, d, J = 8Hz), 6.9 (2H, d, J = 9Hz), 7.49 (2H, d, J = 9Hz), 7.6 (1H, dd, J = 3 ,9Hz), 8.21 (1H, d, J = 2.5Hz)
MS (ESI, m/e) 400 (M+1)

Example 118
2-{4-[3-(cyclopentylmethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethanol
1H NMR (CDCl3, ppm) d 1.30-1.95(8H, m), 2.11(1H, t, J=6.1 Hz), 2.42(1H, 7th, J=7.4 Hz), 3.84(3H, s), 3.89-4.05(2H, m), 4.05-4.15(2H, m), 4.20(2H, d, J=7.1 Hz), 6.75-6.98(4H, m), 7.22-7.35(2H, m), 7.38-7.50(H,),
MS (ESI, m/e) 410(M+1)

Example 119
2-{4-[3-(cyclohexylmethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethanol
1H NMR (CDCl3, ppm) d 0.97-1.40(5H, m), 1.60-1.98(6H, m), 2.08(1H, t, J=6.3 Hz), 3.84(3H, s), 3.90-4.00(2H, m), 4.01-4.20(4H, m), 6.75-6.98(4H, m), 7.18-7.34(2H, m), 7.36-7.49(2H, m), 7.38-7.50(H,),
MS (ESI, m/e) 424(M+1)

Example 120
2-{[5-[4-(2-hydroxyethoxy)phenyl]-1-(4-methoxyphenyl)-1H-

1,2,4-triazol-3-yl]oxy}-1-phenylethanone
1H NMR (CDCl3, ppm) d 2.15(1H, t, J=6.1 Hz), 3.91(3H, s), 3.91-4.01(2H, m), 4.02-4.13(2H, m), 5.61(2H, s), 6.75-6.99(4H, m), 7.19-7.32(2H, m), 7.32-7.69(5H, m), 7.95-8.10(2H, m),
MS (ESI, m/e) 446(M+1)

Example 121
2-{4-[3-isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethanol
1H NMR (CDCl3, ppm) d 1.42(3H, s), 1.45(3H, s), 2.10(1H, t, J=6.1 Hz), 3.90-4.01(5H, m), 4.02-4.15(2H, m), 5.02(1H, 7th, J=6.1 Hz), 6.72-6.95(3H, m), 7.35-7.50(2H, m), 7.57(1H, dd, J=8.8,2.8 Hz), 7.38-7.50(1H, d, J=2.4 Hz),
MS (ESI, m/e) 371(M+1)

Example 122
2-{4-[3-(cyclopropylmethoxy)-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethanol
1H NMR (CDCl3, ppm) d 0.32-0.48(2H, m), 0.56-0.69(2H, m), 1.30-1.48(1H, m), 2.08(1H, t, J=6.7 Hz), 3.96(3H, s), 3.90-4.03(2H, m), 4.05-4.15(2H, m), 4.16(2H, d, J=7.2 Hz), 6.79(1H, d, J=9.1 Hz), 6.82-6.94(2H, m), 7.37-7.49(2H, m), 7.57(1H, dd, J=8.9,2.6 Hz), 8.15(1H, d, J=2.6 Hz),
MS (ESI, m/e) 383(M+1)

Example 123
2-{4-[3-isobutoxy-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethanol
1H NMR (CDCl3, ppm) d 1.05(6H, d, J=6.6 Hz), 2.02-2.29(2H, m), 3.96(3H, s), 3.89-4.04(2H, m), 4.05-4.19(4H, m), 6.79(1H, d, J=8.5 Hz), 6.82-6.92(2H, m), 7.38-7.49(2H, m), 7.58(1H, dd, J=8.7,2.7 Hz), 8.15(1H, d, J=2.8 Hz),
MS (ESI, m/e) 385(M+1)

Example 124
To a dichloromethane solution (5 ml) of

2-{4-[3-(2-ethoxyethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethanol (525 mg, 1.31 mmol) and Et3N (0.275 ml, 1.97 mmol) was added methanesulfonyl chloride (0.153 ml, 1.97 mmol) and stirred at room temperature for 1 hour. 20 mL of water and 10 mL of ethyl acetate were poured into the reaction mixture and the aqueous solution was extracted with ethyl acetate for three times. The combine organic layer was washed with water and brine, and dried over magnesium sulfate. After filtration, the solvent was removed under reduced pressure to give 2-{4-[3-(2-ethoxyethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl methanesulfonate (635 mg, 101%) as a colorless solid.

MS (ESI, m/e) 478 (M+1)

Example 125

A suspention of 2-{4-[3-(2-ethoxyethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl methanesulfonate (630 mg, 1.32 mmol) and potassium phthalimide (367 mg, 1.98 mmol) in dimethylformamide (7 ml) was heated at 60 ℃ for 8 hours. 30 mL of water and 20 mL of ethyl acetate were poured into the reaction mixture and the aqueous solution was extracted with ethyl acetate for three times. The combine organic layer was washed with water and brine, and dried over magnesium sulfate. After filtration, the solvent was removed under reduced pressure. The residue was purified by column chromatography (hexsan/ethyl acetate = 1/1) and eluent was evaporated in vacuo to give 2-(2-{4-[3-(2-ethoxyethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione (565 mg, 81%) as a colorless solid.

1HNMR (200MHz, DMSOd6): 1.13 (3H, t, J = 7Hz), 3.5 (2H, q, J = 7Hz), 3.677 - 3.72 (2H, m), 3.79 (3H, s), 3.95 (2H, t, J = 5.5Hz), 4.22 (2H, t, J = 5.5Hz), 4.314 - 4.36 (2H, m), 6.9 (2H, d, J = 9Hz), 7.01 (2H, d, J = 9Hz), 7.29 (4H, dd, J = 3 ,9Hz), 7.817 - 7.92 (4H, m)

MS (ESI, m/e) 529 (M+1)

Example 126

To a suspention of 2-(2-{4-[3-(2-ethoxyethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione (545 mg, 1.03 mmol) in acetonitrile was added a hydrazine hydrate and heated at 60 ℃ for 2 hours. After filtration, the residual solid was dissolved with chloroform. This chloroform solution was washed with 1N NaOH (aq.), water, and brine, and dried over magnesium sulfate. After filtration, the solvent was removed under reduced pressure to give 2-{4-[3-(2-ethoxyethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethanamine (348 mg, 84.7%) as a colorless oil.

1HNMR (200MHz, CDCl3): 1.23 (3H, t, J = 7Hz), 3.08 (2H, t, J = 5Hz), 3.61 (2H, q, J = 7Hz), 3.8 - 3.82 (2H, m), 3.84 (3H, s), 3.98 (2H, t, J = 5Hz), 4.459 - 4.48 (2H, m), 6.82 (2H, d, J = 9Hz), 6.91 (2H, d, J = 9Hz), 7.26 (2H, d, J = 9Hz), 7.41 (2H, d, J = 9Hz)

MS (ESI, m/e) 399 (M+1)

Example 127

To a dichloromethane solution of (2-{4-[3-(2-ethoxyethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)amine (255 mg, 0.64 mmol) was added a triethylamine and trimethylsilylisocyanide, and stirred at room temperature for 18 hours. 20 mL of water and 10 mL of ethyl acetate were poured into the reaction mixture and the aqueous solution was extracted with ethyl acetate for three times. The combine organic layer was washed with 1N HCl (aq.), water, and brine. This organic solution was dried over magnesium sulfate, and filtrated. After removal of the solvent under reduced pressure, the residual solid was recrystalized from ethanol-water to give N-(2-{4-[3-(2-ethoxyethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea (124 mg, 43.9%) as a colorless solid.

1HNMR (200MHz, CDCl3): 1.23 (3H, t, J = 7Hz), 3.61 (3H, q, J = 6.9Hz), 3.795 - 3.81 (2H, m), 3.98 (2H, t, J = 5.3Hz),

4.457 - 4.48 (2H, m), 5.17 (1H, b.s), 6.76 (2H, d, J = 9Hz), 6.91 (2H, d, J = 9Hz), 7.24 (2H, d, J = 8Hz), 7.38 (2H, d, J = 8.5Hz)
MS (ESI, m/e) 442 (M+1)

The following compound(s) was(were) obtained in a similar manner to that of Example 127.

Example 128

N-(3-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenoxy}propyl)urea
1HNMR (200MHz, DMSOd6): 1.8 (2H, quint, J = 6.3Hz), 3.09 (2H, q, J = 6.4Hz), 3.83 (3H, s), 3.99 (2H, t, J = 6.3Hz), 5.39 (2H, b.s), 6.01 (1H, b.s), 6.97 (2H, d, J = 9Hz), 7.09 (2H, d, J = 9Hz), 7.41 (2H, d, J = 9Hz), 7.47 (2H, d, J = 9Hz)
MS (ESI, m/e) 436 (M+1)

Example 129

N-(2-{4-[3-benzoyl-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea
1HNMR (200MHz, DMSOd6): 3.35 (2H, b.s), 3.83 (3H, s), 3.98 (2H, t, J = 5.8Hz), 5.52 (2H, b.s), 6.16 (1H, b.s), 7.01 (2H, d, J = 9Hz), 7.1 (2H, d, J = 9Hz), 7.439 - 7.72 (7H, m), 8.28 (2H, d, J = 8.5Hz)
MS (ESI, m/e) 458 (M+1)

Example 130

N-(2-{4-[3-isobutyryl-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea
1HNMR (200MHz, CDCl3): 1.29 (6H, d, J = 7Hz), 3.55 - 3.57 (2H, m), 3.79 (1H, sept, J = 6.8Hz), 3.86 (3H, s), 3.97 (2H, t, J = 5.3Hz), 4.61 (2H, b.s), 5.32 (2H, b.s), 6.79 (2H, d, J = 9Hz), 6.95 (2H, d, J = 8.5Hz), 7.29 (2H, d, J = 9Hz), 7.45 (2H, d, J = 9Hz)
MS (ESI, m/e) 424 (M+1)

Example 131

5-(4-{2-[(aminocarbonyl)amino]ethoxy}phenyl)-N-methoxy-1-(6-methoxy-3-pyridinyl)-N-methyl-1H-1,2,4-triazole-3-carboxamide

1HNMR (200MHz, CDCl3): 3.49 (3H, b.s), 3.56 (2H, q, J = 5.9Hz), 3.9 (3H, s), 3.948 - 4 (2H, m), 3.98 (3H, s), 4.59 (2H, b.s), 5.37 (1H, b.s), 6.81 (3H, d, J = 9Hz), 7.43 (2H, d, J = 9Hz), 7.58 (1H, dd, J = 2.8 ,8.5Hz), 8.19 (1H, d, J = 2.5Hz)

MS (ESI, m/e) 442 (M+1)

Example 132

N-(2-{4-[3-isobutyryl-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea

1HNMR (200MHz, DMSOd6): 1.19 (6H, d, J = 7Hz), 3.321 - 3.37 (2H, m), 3.69 (1H, quint, J = 6.8Hz), 3.92 (3H, s), 3.98 (2H, t, J = 5.5Hz), 5.52 (2H, b.s), 6.16 (1H, b.s), 6.985 - 7.04 (3H, m), 7.44 (2H, d, J = 8.5Hz), 7.89 (1H, dd, J = 2.5 ,9Hz), 8.34 (1H, d, J = 2Hz)

MS (ESI, m/e) 425 (M+1)

Example 133

A suspention of 4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenol (1.0 g, 2.97 mmol) in DMF (5 ml) was cooled to 0 ℃, and NaH (155 mg, 3.87 mmol) was added over a 1 min period. After stirring for 1 hour, to this mixture was added a solution of tert-butyl (2-bromoethyl)carbamate (933 mg, 4.16 mmol) in DMF (0.6 ml) and heated at 60 ℃ for 6 hours. 20 mL of water and 20 mL of ethyl acetate were poured into the reaction mixture and the aqueous solution was extracted with ethyl acetate. The combine organic layer was washed with water and brine, and dried over magnesium sulfate. After filtration, the solvent was removed under reduced pressure. The residual oil was purified by column chromatography (ethyl acetate/hexsan =1/4) and eluent was evaporated in vacuo to give tert-butyl (2-{4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)-

carbamate (1.45 g, 101%) as a colorless oil.
1HNMR (200MHz, CDCl3): 1.45 (9H, s), 3.54 (2H, q, J = 5.3Hz), 3.99 (3H, s), 4.04 (2H, t, J = 5.3Hz), 6.85 (1H, d, J = 9Hz), 6.88 (2H, d, J = 8.5Hz), 7.47 (2H, d, J = 9Hz), 7.61 (1H, dd, J = 2.8 ,9Hz), 8.19 (1H, d, J = 3Hz)
MS (ESI, m/e) 480 (M+1)

The following compound(s) was(were) obtained in a similar manner to that of Example 133.

Example 134
tert-butyl (2-{4-[1-(4-methoxyphenyl)-3-(1-piperidinylcarbonyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)-carbamate
MS (ESI, m/e) 522 (M+1)

Example 135
tert-butyl (2-{4-[3-benzoyl-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)carbamate
MS (ESI, m/e) 515 (M+1)

Example 136
tert-butyl (2-{4-[3-isobutyryl-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)carbamate
MS (ESI, m/e) 481 (M+1)

Example 137
tert-butyl (2-{4-[3-{[methoxy(methyl)amino]carbonyl}-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)carbamate
MS (ESI, m/e) 499 (M+1)

Example 138
tert-butyl (2-{4-[3-isobutyryl-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)carbamate
1HNMR (200MHz, CDCl3): 1.3 (6H, d, J = 7Hz), 1.45 (9H, s),

3.54 (2H, q, J = 5.4Hz), 3.78 (1H, sept, J = 6.8Hz), 3.99 (3H, s), 4.04 (2H, t, J = 5Hz), 4.95 (1H, b.s.), 6.84 (1H, d, J = 8Hz), 6.87 (2H, d, J = 9Hz), 7.49 (2H, d, J = 9Hz), 7.61 (1H, dd, J = 2.8 ,9Hz), 8.21 (1H, d, J = 2.5Hz)
MS (ESI, m/e) 482 (M+1)

Example 139

To a solution of (2-{4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)amine (200 mg, 0.527 mmol) in methanol (1 ml) and 1N HCl aq. (3 ml) was added a potassium cyanate and stirred at 50 ℃ for 3 hours. To the reaction mixture was added 4 ml of water and cooled at room temperature. After addition of 1N HCl aq., the residue was filtrated and washed with water several times. The resulting solid was purified by recrystallization from ethanol to give N-(2-{4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea (116 mg, 52.1%) as a colorless crystal.
1HNMR (200MHz, CDCl3): 3.62 (2H, q, J = 5.4Hz), 3.99 (3H, s), 4.07 (2H, t, J = 5Hz), 4.36 (2H, b.s), 6.85 (1H, d, J = 8.5Hz), 6.88 (2H, d, J = 9Hz), 7.47 (2H, d, J = 9Hz), 7.61 (1H, dd, J = 2.8 ,9Hz), 8.19 (1H, d, J = 3Hz)
MS (ESI, m/e) 423 (M+1)

The following compound(s) was(were) obtained in a similar manner to that of Example 139.

Example 140

N-(3-{4-[1-(6-methoxy-3-pyridinyl)-3-(2,2,2-trifluoroethoxy)-1H-1,2,4-triazol-5-yl]phenoxy}propyl)urea
1HNMR (200MHz, DMSO-d6): 1.8 (2H, t, J = 6.3Hz), 3.09 (2H, q, J = 6.3Hz), 3.9 (3H, s), 3.99 (2H, t, J = 6Hz), 5.01 (2H, q, J = 8.9Hz), 5.39 (2H, b.s), 6.01 (1H, b.s), 6.97 (3H, d, J = 9Hz), 7.38 (2H, d, J = 9Hz), 7.82 (1H, dd, J = 2.8 ,9Hz), 8.25 (1H, d, J = 2.5Hz)
MS (ESI, m/e) 467 (M+1)

Example 141

N-(3-{4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenoxy}propyl)urea

1HNMR (200MHz, DMSOd6): 1.8 (2H, t, J = 6.3Hz), 3.1 (2H, q, J = 6.4Hz), 3.82 (3H, s), 4 (2H, t, J = 6Hz), 5.4 (2H, s), 6.02 (1H, t, J = 5.8Hz), 7.01 (3H, dd, J = 2.5 ,9Hz), 7.44 (2H, d, J = 8.5Hz), 7.94 (1H, dd, J = 2.8 ,8.5Hz), 8.38 (1H, d, J = 2.5Hz)

MS (ESI, m/e) 437 (M+1)

Example 142

N-(2-{4-[1-(4-methoxyphenyl)-3-(1-piperidinylcarbonyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea

1HNMR (200MHz, DMSOd6): 1.56 (6H, b), 3.281 - 3.36 (2H, m), 3.63 (4H, b), 3.82 (3H, s), 3.96 (2H, t, J = 5.5Hz), 5.52 (2H, s), 6.15 (1H, t, J = 5.8Hz), 6.98 (2H, d, J = 8.5Hz), 7.07 (2H, d, J = 9Hz), 7.39 (4H, d, J = 8.5Hz)

MS (ESI, m/e) 465 (M+1)

Example 143

tert-butyl (2-{4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)-carbamate (1.45 g, 3.02 mmol) was dissolved in 4n HCl dioxane solution (4 ml), and stirred at 0 ℃ for 30 min. To this reaction mixture was added a dioxane (6 ml) and stirred at room temperature for 1 hour. 50 ml of 1N HCl aq. and 50 ml of ethyl acetate was poured to this mixture and extracted with water. The water solution was neutralized by an aqueous solution of potassium carbonate and extracted with ethyl acetate for three times. The combine organic layer was washed with water and brine and dried over magnesium sulfate. After filtration, the solvent was removed in vacuo, and the residual oil was purified by recrystallization from IPE-hexsan to give 2-{4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethanamine (743 mg, 64.8%) as a pale brown crystal.

1HNMR (200MHz, CDCl3): 3.1 (2H, t, J = 5.1Hz), 3.99 (3H, s), 4.02 (2H, t, J = 4.5Hz), 6.84 (1H, d, J = 8.5Hz), 6.9 (2H, d, J = 9Hz), 7.47 (2H, d, J = 9Hz), 7.61 (1H, dd, J = 2.8 ,8.5Hz), 8.2 (1H, d, J = 2.5Hz)
MS (ESI, m/e) 380 (M+1)

The following compound(s) was(were) obtained in a similar manner to that of Example 143.

Example 144
(3-{4-[1-(6-methoxy-3-pyridinyl)-3-(2,2,2-trifluoroethoxy)-1H-1,2,4-triazol-5-yl]phenoxy}propyl)amine
MS (ESI, m/e) 424 (M+1)

Example 145
A mixture of 4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenol (200 mg, 0.595 mmol), potassium carbonate (493 mg, 3.57 mmol), potassium Iodide (296 mg, 1.78 mmol) and 3-chloro-1-propanol (0.298 mL, 3.57 mmol) in dimethylformamide (4 mL) was stirred at 75 ℃ for 18 hours. 20 mL of water and 20 mL of ethyl acetate were poured into the reaction mixture and the aqueous solution was extracted with ethyl acetate for three times. The combine organic layer was washed with water and brine, and dried over magnesium sulfate. After filtration, the solvent was removed under reduced pressure. The residue was purified by column chromatography (hexsan/ethyl acetate 1/1) and eluent was evaporated. The residual solid was purified by recrystallization from IPE-hexsan to give 3-{4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenoxy}-1-propanol (160 mg, 68.2%) as a colorless crystal.
1HNMR (200MHz, CDCl3): 2.06 (2H, quint, J = 6Hz), 3.832 - 3.9 (2H, m), 3.99 (3H, s), 4.14 (2H, t, J = 6Hz), 6.84 (1H, d, J = 9Hz), 6.89 (2H, d, J = 9Hz), 7.46 (2H, d, J = 9Hz), 7.61 (1H, dd, J = 2.8 ,9Hz), 8.2 (1H, d, J = 2.5Hz)
MS (ESI, m/e) 395 (M+1)

The following compound(s) was(were) obtained in a similar manner to that of Example 145.

Example 146

3-{4-[1-(6-methoxy-3-pyridinyl)-3-(2,2,2-trifluoroethoxy)-1H-1,2,4-triazol-5-yl]phenoxy}-1-propanol

1HNMR (200MHz, CDCl3): 2.05 (2H, t, J = 5.8Hz), 3.86 (2H, b.s), 3.97 (3H, s), 4.13 (2H, t, J = 6Hz), 4.75 (2H, q, J = 8.2Hz), 6.81 (1H, d, J = 9.5Hz), 6.87 (2H, d, J = 9Hz), 7.42 (2H, d, J = 9Hz), 7.57 (1H, dd, J = 2.8 ,8.5Hz), 8.15 (1H, d, J = 2Hz)

MS (ESI, m/e) 425 (M+1)

Example 147

3-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenoxy}-1-propanol

1HNMR (200MHz, CDCl3): 2.05 (2H, quint, J = 6Hz), 3.817 - 3.9 (2H, m), 3.87 (3H, s), 4.13 (2H, t, J = 6Hz), 6.86 (2H, d, J = 9Hz), 6.96 (2H, d, J = 9Hz), 7.3 (2H, d, J = 9Hz), 7.46 (2H, d, J = 9Hz)

MS (ESI, m/e) 394 (M+1)

Example 148

To a dichloromethane solution (2 ml) of (2-{4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)amine (200 mg, 0.527 mmol) and Et3N (88.2 ul, 0.633 mmol) was added methanesulfonyl chloride (49 ul, 0.633 mmol) and stirred at room temperature for 3 hours. 20 mL of water and 20 mL of ethyl acetate were poured into the reaction mixture and the aqueous solution was extracted with ethyl acetate. The combine organic layer was washed with 0.1N HCl aq. and brine, and dried over magnesium sulfate. After filtration, the solvent was removed under reduced pressure. The residual solid was purifyied by recrystallization from ethanol to give N-(2-{4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-

1,2,4-triazol-5-yl]phenoxy}ethyl)methanesulfonamide (196 mg, 81.3%) as a colorless solid.
1HNMR (200MHz, CDCl3): 3.03 (3H, s), 3.56 (2H, q, J = 5.4Hz), 4 (3H, s), 4.13 (2H, t, J = 5Hz), 4.76 (1H, b.s), 6.85 (1H, d, J = 8.5Hz), 6.88 (2H, d, J = 8.5Hz), 7.49 (2H, d, J = 9Hz), 7.61 (1H, dd, J = 2.8 ,9Hz), 8.2 (1H, d, J = 2Hz)
MS (ESI, m/e) 458 (M+1)

The following compound(s) was(were) obtained in a similar manner to that of Example 148.

Example 149
N-(3-{4-[1-(6-methoxy-3-pyridinyl)-3-(2,2,2-trifluoroethoxy)-1H-1,2,4-triazol-5-yl]phenoxy}propyl)-methanesulfonamide
1HNMR (200MHz, DMSO-d6): 1.89 (2H, t, J = 6.5Hz), 3.09 (2H, q, J = 6.7Hz), 3.33 (3H, s), 3.89 (3H, s), 4.04 (2H, t, J = 6.3Hz), 4.99 (2H, t, J = 8.8Hz), 6.98 (2H, dd, J = 1.5 ,8.5Hz), 7.06 (1H, t, J = 5.8Hz), 7.39 (2H, d, J = 9Hz), 7.82 (1H, dd, J = 2.8 ,8.5Hz), 8.25 (1H, d, J = 3Hz)
MS (ESI, m/e) 502 (M+1)

Example 150
N-(3-{4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenoxy}propyl)methanesulfonamide
1HNMR (200MHz, DMSOd6): 1.9 (2H, t, J = 6.5Hz), 3.09 (2H, q, J = 6.5Hz), 3.33 (6H, s), 4.06 (2H, t, J = 6.3Hz), 6.99 - 7.07 (3H, m), 7.45 (2H, d, J = 8.5Hz), 7.94 (1H, dd, J = 2.8 ,8.5Hz), 8.38 (1H, d, J = 2.5Hz)
MS (ESI, m/e) 472 (M+1)

Example 151
N-(3-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenoxy}propyl)methanesulfonamide
1HNMR (200MHz, DMSOd6): 1.89 (2H, t, J = 6.5Hz), 3.09 (2H, t, J = 6.8Hz), 3.33 (3H, s), 3.83 (3H, s), 4.05 (2H, t, J

= 6Hz), 6.98 (2H, d, J = 9Hz), 7.09 (2H, d, J = 9Hz), 7.42 (2H, d, J = 10Hz), 7.47 (2H, d, J = 9Hz)
MS (ESI, m/e) 471 (M+1)

Example 152
N-(2-{4-[1-(4-methoxyphenyl)-3-(1-piperidinylcarbonyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)methanesulfonamide
1HNMR (200MHz, DMSOd6): 1.56 (6H, b), 2.94 (3H, s), 3.298 - 3.35 (2H, m), 3.63 (4H, b), 3.82 (3H, s), 4.05 (2H, t, J = 5.5Hz), 6.98 (2H, d, J = 8.5Hz), 7.07 (2H, d, J = 9Hz), 7.28 (1H, b.s), 7.39 (2H, d, J = 9Hz), 7.4 (2H, d, J = 9Hz)
MS (ESI, m/e) 500 (M+1)

Example 153
N-(2-{4-[3-benzoyl-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)methanesulfonamide
1HNMR (200MHz, DMSOd6): 2.95 (3H, s), 3.324 - (2H, m), 3.83 (3H, s), 4.06 (2H, t, J = 5.3Hz), 7.02 (2H, d, J = 9Hz), 7.1 (2H, d, J = 9Hz), 7.29 (1H, b.s), 7.449 - 7.51 (4H, m), 7.59 (2H, t, J = 7.3Hz), 7.72 (1H, t, J = 7.3Hz), 8.29 (2H, d, J = 7Hz)
MS (ESI, m/e) 493 (M+1)

Example 154
N-(2-{4-[3-isobutyryl-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)methanesulfonamide
1HNMR (200MHz, CDCl3): 1.29 (6H, d, J = 7Hz), 3.512 - 3.59 (2H, m), 3.79 (1H, sept, J = 6.8Hz), 3.87 (3H, s), 4.11 (2H, t, J = 5Hz), 6.83 (2H, d, J = 9Hz), 6.97 (2H, d, J = 9Hz), 7.31 (2H, d, J = 9Hz), 7.5 (2H, d, J = 8.5Hz)
MS (ESI, m/e) 459 (M+1)

Example 155
N-methoxy-1-(6-methoxy-3-pyridinyl)-N-methyl-5-(4-{2-[(methylsulfonyl)amino]ethoxy}phenyl)-1H-1,2,4-triazole-3-carboxamide

1HNMR (200MHz, CDCl3): 3.03 (3H, s), 3.48 (3H, b.s), 3.56 (2H, q, J = 5.4Hz), 3.91 (3H, s), 3.91 (3H, s), 4.098 - 4.15 (2H, m), 4.79 (1H, b.s), 6.807 - 6.89 (3H, m), 7.49 (7H, d, J = 9Hz), 7.6 (1H, dd, J = 2.5 ,9Hz), 8.2 (1H, d, J = 2.5Hz)
MS (ESI, m/e) 477 (M+1)

Example 156

A suspention of 4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenol (1.0 g, 2.97 mmol) in DMF (5 ml) was cooled to 0 ℃, and NaH (155 mg, 3.87 mmol) was added over a 1 min period. After stirring for 1 hour, to this mixture was added a solution of tert-butyl (3-bromopropyl)carbamate (991 mg, 4.16 mmol) in DMF (0.6 ml) and heated at 60 ℃ for 6 hours. 20 mL of water and 20 mL of ethyl acetate were poured into the reaction mixture and the aqueous solution was extracted with ethyl acetate. The combine organic layer was washed with water and brine, and dried over magnesium sulfate. After filtration, the solvent was removed under reduced pressure. The residual oil was purified by column chromatography (ethyl acetate/hexsan =1/4 => 1/1) and eluent was evaporated in vacuo to give tert-butyl (3-{4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenoxy}propyl)-carbamate (1.45 g, 98.8%) as a colorless oil.
1HNMR (200MHz, CDCl3): 1.44 (9H, s), 1.99 (2H, quint, J = 6.3Hz), 3.32 (2H, q, J = 6.5Hz), 3.99 (3H, s), 4.03 (2H, t, J = 6Hz), 4.72 (1H, b.s), 6.84 (1H, d, J = 9Hz), 6.87 (2H, d, J = 9Hz), 7.46 (2H, d, J = 8.5Hz), 7.61 (1H, dd, J = 2.8 ,9Hz), 8.2 (1H, d, J = 2.5Hz)
MS (ESI, m/e) 494 (M+1)

The following compound(s) was(were) obtained in a similar manner to that of Example 156.

Example 157

tert-butyl (3-{4-[1-(6-methoxy-3-pyridinyl)-3-(2,2,2-trifluoroethoxy)-1H-1,2,4-triazol-5-

yl]phenoxy}propyl)carbamate
1HNMR (200MHz, CDCl3): 1.44 (9H, s), 1.98 (2H, t, J = 6.3Hz), 3.32 (2H, q, J = 6.4Hz), 3.97 (3H, s), 4.02 (2H, t, J = 6Hz), 4.75 (2H, q, J = 8.2Hz), 6.784 - 6.87 (3H, m), 7.42 (2H, d, J = 9Hz), 7.57 (1H, dd, J = 2.8 ,8.5Hz), 8.15 (1H, d, J = 2.5Hz)
MS (ESI, m/e) 524 (M+1)

Example 158

tert-butyl (3-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenoxy}propyl)carbamate
1HNMR (200MHz, CDCl3): 1.44 (9H, s), 1.98 (2H, t, J = 6.5Hz), 3.32 (2H, q, J = 6.4Hz), 3.87 (3H, s), 4.02 (2H, t, J = 6Hz), 6.84 (2H, d, J = 9Hz), 6.96 (2H, d, J = 9Hz), 7.31 (2H, d, J = 9Hz), 7.46 (2H, d, J = 8.5Hz)
MS (ESI, m/e) 493 (M+1)

Example 159

tert-butyl (3-{4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenoxy}propyl)-carbamate (448 mg, 0.908 mmol) was dissolved in 4n HCl dioxane solution (4 ml), and stirred at 0 ℃ for 30 min. To this reaction mixture was added a dioxane (6 ml) and stirred at room temperature for 1 hour. The resulting solid was filtrated and dried over in vaccuo to give (3-{4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenoxy}propyl)-amine hydrochloride (400 mg, 94.5 mmol) as a colorless solid.
MS (ESI, m/e) 394 (M+1)
The following compound(s) was(were) obtained in a similar manner to that of Example 159.

Example 160

(3-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenoxy}propyl)amine hydrochloride
1HNMR (200MHz, DMSOd6): 2.01 (2H, t, J = 6.8Hz), 2.94 (2H, t, J = 7.3Hz), 3.83 (3H, s), 4.09 (2H, t, J = 6Hz), 6.99

(2H, d, J = 9Hz), 7.09 (2H, d, J = 9Hz), 7.45 (4H, t, J = 8.3Hz)
MS (ESI, m/e) 393 (M+1)

Example 161
(2-{4-[1-(4-methoxyphenyl)-3-(1-piperidinylcarbonyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)amine hydrochloride
1HNMR (200MHz, DMSOd6): 1.56 (6H, b.s), 3.2 (2H, q, J = 5.1Hz), 3.63 (4H, b.s), 3.82 (3H, s), 4.2 (2H, t, J = 5Hz), 7.02 (2H, d, J = 9Hz), 7.07 (2H, d, J = 9Hz), 7.39 (2H, d, J = 8.5Hz), 7.43 (2H, d, J = 9Hz), 8.2 (2H, b.s)
MS (ESI, m/e) 458 (M+1)

Example 162
[5-[4-(2-aminoethoxy)phenyl]-1-(4-methoxyphenyl)-1H-1,2,4-triazol-3-yl](phenyl)methanone hydrochloride
MS (ESI, m/e) 415 (M+1)

Example 163
1-[5-[4-(2-aminoethoxy)phenyl]-1-(4-methoxyphenyl)-1H-1,2,4-triazol-3-yl]-2-methyl-1-propanone hydrochloride
MS (ESI, m/e) 381 (M+1)

Example 164
5-[4-(2-aminoethoxy)phenyl]-N-methoxy-1-(6-methoxy-3-pyridinyl)-N-methyl-1H-1,2,4-triazole-3-carboxamide dihydrochloride
MS (ESI, m/e) 399 (M+1)

Example 165
1-[5-[4-(2-aminoethoxy)phenyl]-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-3-yl]-2-methyl-1-propanone dihydrochloride
MS (ESI, m/e) 382 (M+1)

Example 166
To a solution of 4-[3-(cyclopentylmethoxy)-1-

(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenol in dimethylformamide (2 ml), potassium carbonate (386 mg, 2.79 mmol), potassium iodide (77 mg, 0.465 mmol) and N-(2-bromoethyl)urea (155 mg, 0.93 mmol) were added. The mixture was heated at 120℃ for 7.5 hours. Then N-(2-bromoethyl)urea (91 mg, 54 mmol) was added to the mixture per 1 hour at 5 times. After cooling, ethyl acetate and water were poured into the mixture. The organic layer was separated, washed with water and brine and dried over magnesium sulfate. The solvent was removed under reduced pressure. The residue was purified by silicagel chromatografy (dichloromethane-methanol 15:1). The desired product N-(2-{4-[3-(cyclopentylmethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea was isolated by filtration, washed with isopropylether and dried in vacuo. (146 mg, 69% yield)

1H NMR (DMSO-d6, ppm) d 1.18-1.90(8H, m), 2.26-2.48(2H, m), 3.25-3.40(2H, m), 3.80(3H, s), 3.95(2H, bt, J=5.5 Hz), 4.11(2H, d, J=7.1 Hz), 5.52(2H, bs), 6.15(1H, bt, J=5.7 Hz), 6.88-7.11(4H, m), 7.21-7.42(4H, m),

MS (ESI, m/e) 452(M+1)

The following compound(s) was(were) obtained in a similar manner to that of Example 166.

Example 167

N-(2-{4-[3-(cyclohexylmethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea

1H NMR (DMSO-d6, ppm) d 0.90-1.41(5H, m), 1.52-1.89(6H, m), 3.25-3.40(2H, m), 3.80(3H, s), 3.95(2H, t, J=5.5 Hz), 4.05(2H, d, J=5.9 Hz), 5.52(2H, bs), 6.14(1H, bt, J=5.7 Hz), 6.90-7.10(4H, m), 7.25-7.45(4H, m),

MS (ESI, m/e) 466(M+1)

Example 168

N-(2-{4-[1-(4-methoxyphenyl)-3-(2-oxo-2-phenylethoxy)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea

1H NMR (DMSO-d6, ppm) d 3.25-3.40(2H, m), 3.79(3H, s), 3.94(2H, t, J=2.6 Hz), 5.51(2H, bs), 5.74(2H, s), 6.10-6.21(1H, m), 6.89-7.09(4H, m), 7.21-7.39(4H, m), 7.52-7.78(3H, m), 7.95-8.08(2H, m),
MS (ESI, m/e) 488(M+1)

Example 169

N-(2-{4-[3-isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea
1H NMR (DMSO-d6, ppm) d 1.35(6H, d), 3.24-3.41(2H, m), 3.89(3H, s), 3.96(2H, bt, J=5.5 Hz), 4.91(1H, 7th), 5.52(2H, bs), 6.15(1H, bt, J=5.7 Hz), 6.91-7.08(3H, m), 7.36(2H, d, J=8.8 Hz), 7.78(1H, dd, J=8.7,2.7 Hz), 8.21(1H, d, J=2.5 Hz),
MS (ESI, m/e) 413(M+1)

Example 170

N-(2-{4-[3-(cyclopropylmethoxy)-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea
1H NMR (DMSO-d6, ppm) d 0.30-0.45(2H, m), 0.50-0.68(2H, m), 1.19-1.40(1H, m), 3.25-3.42(2H, m), 3.89(3H, s), 3.96(2H, bt, J=5.5 Hz), 4.09(2H, d, J=7.2 Hz), 5.52(2H, bs), 6.15(1H, bt, J=5.6 Hz), 6.89-7.07(3H, m), 7.36(2H, d, J=8.8 Hz), 7.77(1H, dd, J=8.9,2.7 Hz), 8.21(1H, d, J=2.6 Hz),
MS (ESI, m/e) 425(M+1)

Example 171

N-(2-{4-[3-isobutoxy-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea
1H NMR (DMSO-d6, ppm) d 0.98(6H, d, J=6.7 Hz), 1.91-2.20(1H, m), 3.25-3.40(2H, m), 3.89(3H, s), 3.96(2H, bt, J=5.5 Hz), 4.03(2H, d, J=6.5 Hz), 5.52(2H, bs), 6.15(1H, bt, J=5.6 Hz), 6.89-7.08(3H, m), 7.37(2H, d, J=8.8 Hz), 7.78(1H, dd, J=8.8,2.7 Hz), 8.21(1H, d, J=2.6 Hz),
MS (ESI, m/e) 427(M+1)

Example 172

Under ice-bath cooling, lithium aluminium hydride was added to the solution of 4-[3-(cyclopentyloxy)-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]benzonitrile in THF (8 ml) and stirred for 5 min. The solution was stirred for 1hr at room temperature. The mixture was poured into the saturated ammonium chloride, extracted with EtOAc, washed with water and brine and dried over sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by silicagel chromatography (dichloromethane-methanol 10:1). The desired product 1-{4-[3-(cyclopentyloxy)-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenyl}methanamine was isolated as yellow oil. (470 mg, 63% yield)

1H NMR (CDCl3, ppm) d 1.47-2.08(8H, m), 3.84(2H, s), 3.96(3H, s), 5.14-5.29(1H, m), 6.79(1H, d, J=9 Hz), 7.21-7.37(2H, m), 7.40-7.50(2H, m), 7.58(1H, dd, J=8.7,2.7 Hz), 8.14(1H, d, J=2.4 Hz),

MS (ESI, m/e) 366(M+1)

Example 173

Under ice-bath-cooling, a mixture of {4-[3-(cyclopentyloxy)-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]benzyl}amine (50 mg, 0.137 mmol), Et3N (21 mg, 0.205 mmol) and methanesulfonyl chloride (24 mg, 0.205 mmol) in dichloromethane (0.5 ml) was stirred for 7 hr at same temperature. Water and ethyl acetate were added to the mixture and the organic layer was separated, washed with 0.1 N-HCl, water and brine, and dried over magnesium sulfate. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane-methanol 10:1). The desired product N-{4-[3-(cyclopentyloxy)-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]benzyl}methanesulfonamide was isolated by filtration ,washed with isopropylether and dried in vacuo. (31 mg, 51% yield)

1H NMR (CDCl3, ppm) d 1.55-2.08(8H, m), 2.91(3H, s), 3.96(3H, s), 4.33(2H, d, J=6.2 Hz), 4.80(1H, bt, J=6.1 Hz), 5.25-5.29(1H, m), 6.8(1H, d, J=9.1 Hz), 7.28-7.38(2H, m), 7.40-7.54(2H, m),

7.58(1H, dd, J=8.6,2.7 Hz), 8.10(1H, d, J=2.8 Hz),
MS (ESI, m/e) 444(M+1)

Example 174

To a solution of {4-[3-(cyclopentyloxy)-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]benzyl}amine (320 mg, 0.88 mmol) and Et3N (354 mg, 3.5 mmol) in dichloromethane (3 ml), was added trimethylsilyl isocyanate (303 mg,2.63 mmol). The mixture was stirred for 7hr at room temperature. Then ethyl acetate and water were poured into the mixture. The organic layer was separated, washed with 0.1N-HCl, water and brine and dried over magnesium sulfate. The solvent was removed under reduced pressure. The residue was purified by silicagel chromatography (dichloromethane-methanol 15:1). The desired product N-{4-[3-(cyclopentyloxy)-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]benzyl}urea was isolated by filtration ,washed with isopropylether and dried in vacuo. (145 mg, 40% yield)
1H NMR (DMSO-d6, ppm) d 1.51-2.00(8H, m), 3.89(3H, s), 4.18(2H, d, J=6.1 Hz), 5.08-5.21(1H, m), 5.55(2H, s), 6.45(1H, bt, J=6.1 Hz), 6.94(1H, d, J=9.0 Hz), 7.20-7.48(4H, m), 7.78(1H, dd, J=8.9,2.7 Hz), 8.2(1H, d, J=2.6 Hz),
MS (ESI, m/e) 409(M+1)

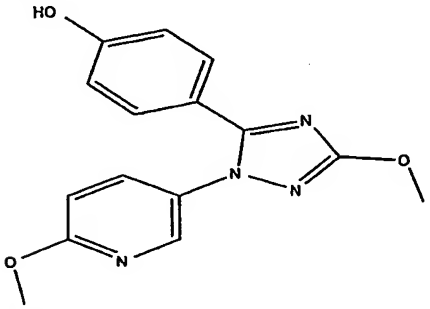
(continued to the next page)

Preparation 122

The following compound was obtained in substantially the same manner as that of Preparation 43.

P122

4-[3-methoxy-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenol



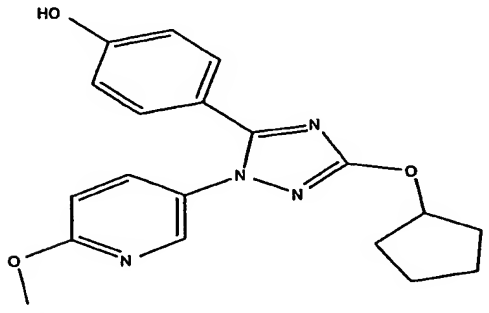
1H NMR (CDCl3, ppm) d 3.89(3H, s), 3.93(3H, s), 6.69-6.83(2H, m), 6.95(1H, d, J=8.9 Hz), 7.20-7.32(2H, m), 7.77(1H, dd, J=8.8,2.8 Hz), 8.20(1H, d, J=2.4 Hz), 10.0(1H, bs),
MS (ESI, m/e) 299(M+1)

Preparation 123

The following compound was obtained in substantially the same manner as that of Preparation 43.

P123

4-[3-(cyclopentyloxy)-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenol



1H NMR (DMSO-d6, ppm) d 1.50-1.98(8H, m), 3.89(3H, s), 5.05-5.19(1H, m), 6.69-6.82(2H, m), 6.94(1H, d, J=8.9 Hz), 7.18-7.30(2H, m), 7.76(1H, dd, J=8.8,2.6 Hz), 8.19(1H, d, J=2.6

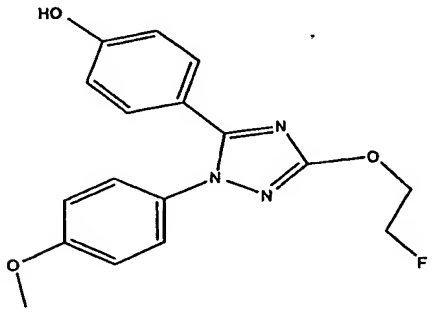
Hz), 10.05(1H, bs),
MS (ESI, m/e) 353(M+1)

Preparation 124

The following compound was obtained in substantially the same manner as that of Preparation 43.

P124

4-[3-(2-fluoroethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenol



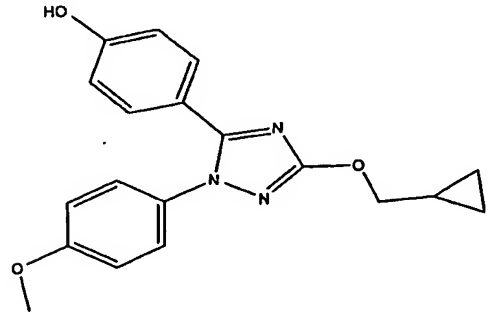
1H NMR (CDCl3, ppm) d 3.80(3H, s), 4.33-4.77(1H, m), 4.50-4.70(2H, m), 4.80-4.93(1H, m), 6.67-6.80(2H, m), 6.97-7.08(2H, m), 7.18-7.34(4H, m), 9.97(1H, bs),
MS (ESI, m/e) 330(M+1)

Preparation 125

The following compound was obtained in substantially the same manner as that of Preparation 43.

P125

4-[3-(cyclopropylmethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenol



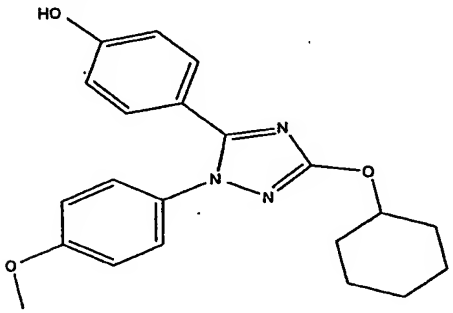
1H NMR (DMSO-d6, ppm) d 0.28-0.42(2H, m), 0.49-0.65(2H, m), 1.19-1.38(1H, m), 3.78(3H, s), 4.06(2H, d, J=7.1 Hz), 6.67-6.79(2H, m), 6.96-7.08(2H, m), 7.15-7.37(4H, m), 9.99(1H, bs),
MS (ESI, m/e) 338(M+1)

Preparation 126

The following compound was obtained in substantially the same manner as that of Preparation 43.

P126

4-[3-(cyclohexyloxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenol



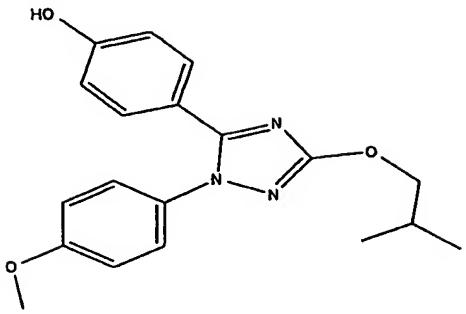
1H NMR (DMSO-d6, ppm) d 1.19-2.11(10H, m), 3.80(3H, s), 4.64(1H, 5th, J=4.2Hz), 6.66-6.79(2H, m), 6.92-7.08(2H, m), 7.15-7.35(4H, m), 10.00(1H, bs),
MS (ESI, m/e) 366(M+1)

Preparation 127

The following compound was obtained in substantially the same manner as that of Preparation 43.

P127

4-[3-isobutoxy-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenol



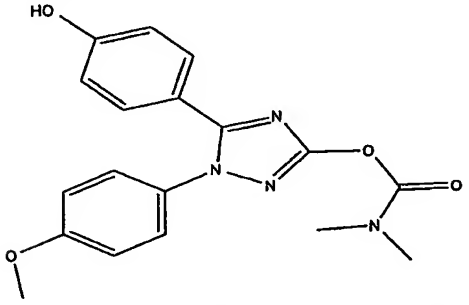
1H NMR (DMSO-d6, ppm) d 0.98(6H, d, J=6.8 Hz), 1.94-2.21(1H, m), 3.80(3H, s), 4.00(2H, d, J=6.6 Hz), 6.72(2H, d, J=8.6 Hz), 6.95-7.08(2H, m), 7.18-7.40(4H, m), 10.06(1H, bs),
MS (ESI, m/e) 340(M+1)

Preparation 128

The following compound was obtained in substantially the same manner as that of Preparation 43.

P128

5-(4-hydroxyphenyl)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-3-yl dimethylcarbamate



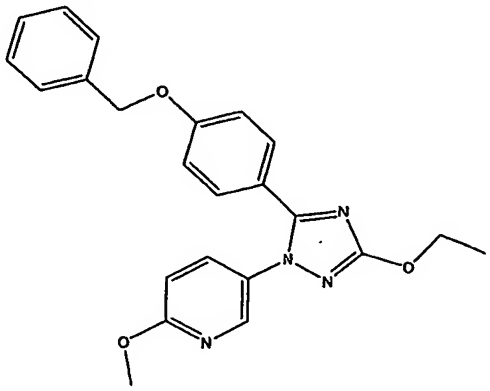
1H NMR (DMSO-d6, ppm) d 2.94(3H, s), 3.07(3H, s), 3.81(3H, 3), 6.71-6.78(2H, m), 7.00-7.08(2H, m), 7.20-7.28(2H, m), 7.29-7.37(2H, m), 10.09(1H, bs),
MS (ESI, m/e) 355(M+1)

Preparation 129

The following compound was obtained in substantially the same manner as that of Preparation 40.

P129

5-{5-[4-(benzyloxy)phenyl]-3-ethoxy-1H-1,2,4-triazol-1-yl}-2-methoxypyridine



1H NMR (CDCl3, ppm) d 1.46(3H, t, J=7.1 Hz), 3.96(3H, s), 4.39(2H, q, J=7.1 Hz), 5.06(2H, s), 6.78(1H, d, J=9.1 Hz), 6.86-6.98(2H, m), 7.29-7.49(7H, m), 7.57(1H, dd, J=8.9,2.6 Hz), 8.16(1H, d, J=3.0 Hz),

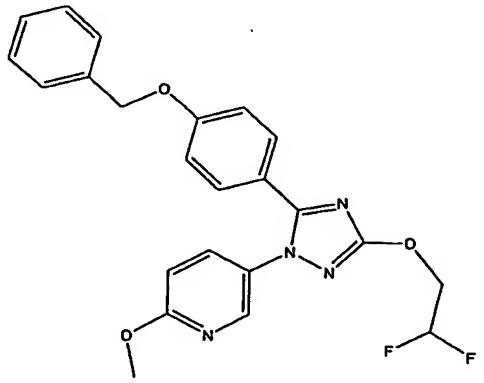
MS (ESI, m/e) 403(M+1)

Preparation 130

The following compound was obtained in substantially the same manner as that of Preparation 40.

P130

5-[5-[4-(benzyloxy)phenyl]-3-(2,2-difluoroethoxy)-1H-1,2,4-triazol-1-yl]-2-methoxypyridine



1H NMR (DMSO-d6, ppm) d 3.90(3H, s), 4.58(2H, td, J=14.9,3.40 Hz), 5.12(2H, s), 6.44(1H, tt, J=54.3,3.4 Hz), 6.90-7.12(3H, m), 7.31-7.50(7H, m), 7.82(1H, dd, J=8.8,2.7 Hz), 8.25(1H, d, J=2.7 Hz),

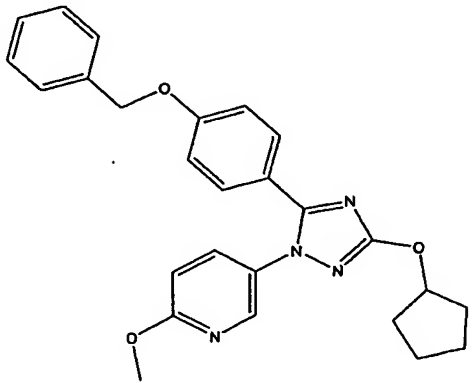
MS (ESI, m/e) 439(M+1)

Preparation 131

The following compound was obtained in substantially the same manner as that of Preparation 40.

P131

5-[5-[4-(benzyloxy)phenyl]-3-(cyclopentyloxy)-1H-1,2,4-triazol-1-yl]-2-methoxypyridine



1H NMR (DMSO-d6, ppm) d 1.50-2.00(8H, m), 3.89(3H, s), 5.05-5.20(3H, m), 6.95(1H, d, J=9.0 Hz), 7.04(2H, d, J=8.9 Hz), 7.30-7.50(7H, m), 7.79(1H, dd, J=8.9,2.7 Hz), 8.21(1H, d, J=2.5 Hz),

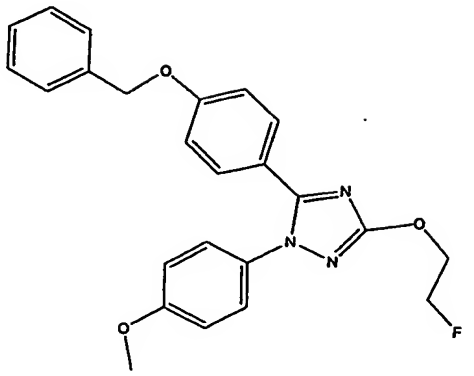
MS (ESI, m/e) 443(M+1)

Preparation 132

The following compound was obtained in substantially the same manner as that of Preparation 40.

P132

5-[4-(benzyloxy)phenyl]-3-(2-fluoroethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazole



1H NMR (CDCl3, ppm) d 3.84 (3H, s), 4.47-4.58 (1H, m), 4.60-4.72 (2H, m), 4.85-4.95 (1H, m), 5.05 (2H, s), 6.82-7.00 (4H, m), 7.20-7.50 (9H, m),

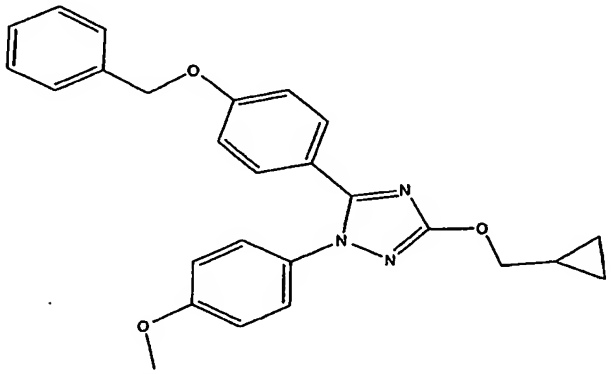
MS (ESI, m/e) 420 (M+1)

Preparation 133

The following compound was obtained in substantially the same manner as that of Preparation 40.

P133

5-[4-(benzyloxy)phenyl]-3-(cyclopropylmethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazole



1H NMR (DMSO-d6, ppm) d 0.29-0.41 (2H, m), 0.50-0.66 (2H, m), 1.19-1.39 (1H, m), 3.80 (3H, s), 4.07 (2H, d, J=7.2 Hz), 5.10 (2H, s), 7.02 (4H, d, J=8.8 Hz), 7.25-7.50 (9H, m),

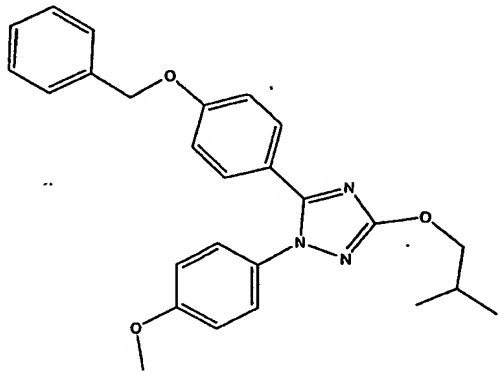
MS (ESI, m/e) 428 (M+1)

Preparation 134

The following compound was obtained in substantially the same manner as that of Preparation 40.

P134

5-[4-(benzyloxy)phenyl]-3-isobutoxy-1-(4-methoxyphenyl)-1H-1,2,4-triazole



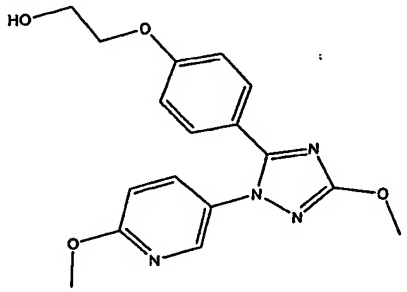
1H NMR (DMSO-d6, ppm) d 0.98(6H, d, J=6.7 Hz), 1.92-2.19(1H, m), 3.80(3H, s), 4.01(2H, d, J=6.5 Hz), 5.10(2H, s), 6.90-7.10(4H, m), 7.25-7.49(9H, m),
MS (ESI, m/e) 430(M+1)

Example 175

The following compound was obtained in substantially the same manner as that of Example 113.

E175

2-{4-[3-methoxy-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethanol



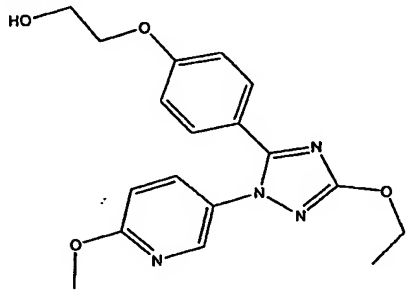
1H NMR (CDCl3, ppm) d 2.18(1H, t, J=6.1 Hz), 3.89-4.04(5H, m), 4.03-4.15(5H, m), 6.75-6.94(3H, m), 7.36-7.49(2H, m), 7.57(1H, dd, J=8.8,2.6 Hz), 8.15(1H, d, J=2.4 Hz),
MS (ESI, m/e) 342(M+1)

Example 176

The following compound was obtained in substantially the same manner as that of Example 113.

E176

2-{4-[3-ethoxy-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethanol



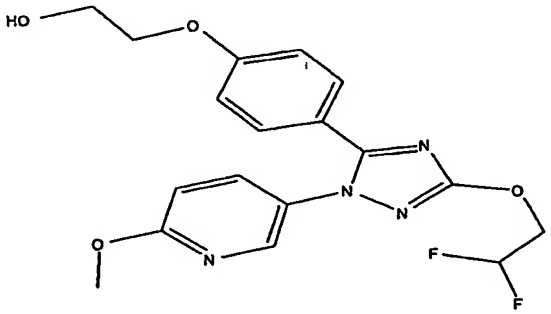
1H NMR (CDCl3, ppm) d 1.46(3H, t, J=7.0 Hz), 2.15(3H, t, J=6.2 Hz), 3.89-4.04(5H, m), 4.05-4.15(2H, m), 4.39(2H, q, J=7.0 Hz), 6.71-6.93(3H, m), 7.37-7.49(2H, m), 7.57(1H, dd, J=8.8,2.8 Hz), 8.15(1H, d, J=2.4 Hz),
MS (ESI, m/e) 357(M+1)

Example 177

The following compound was obtained in substantially the same manner as that of Example 113.

E177

2-{4-[3-(2,2-difluoroethoxy)-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]-phenoxy}ethanol



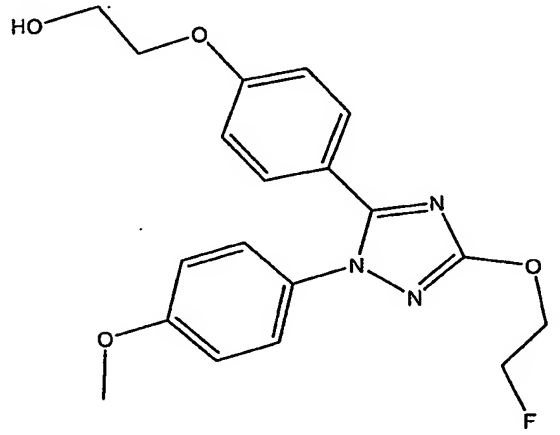
1H NMR (CDCl3, ppm) d 2.12(1H, t, J=6.2 Hz), 3.89-4.03(5H, m), 4.05-4.15(2H, m), 4.55(2H, td, J=13.0,4.3 Hz), 6.18(1H, tt,

J=55.2,4.2 Hz), 6.76-6.95(3H, m), 7.37-7.49(2H, m), 7.57(1H, dd, J=8.8,2.7 Hz), 8.15(1H, d, J=2.6 Hz),
MS (ESI, m/e) 393(M+1)

Example 178

The following compound was obtained in substantially the same manner as that of Example 113.

E178



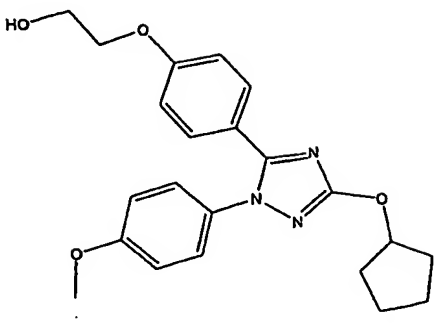
1H NMR (CDCl3, ppm) d 2.17(1H, t, J=6.0 Hz), 3.84(3H, s), 3.89-4.02(2H, m), 4.02-4.12(2H, m), 4.46-4.58(1H, m), 4.60-4.73(2H, m), 4.85-4.94(1H, m), 6.79-6.98(4H, m), 7.21-7.32(2H, m), 7.37-7.47(2H, m),
MS (ESI, m/e) 374(M+1)

Example 179

The following compound was obtained in substantially the same manner as that of Example 113.

E179

2-{4-[3-(cyclopentyloxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}-ethanol



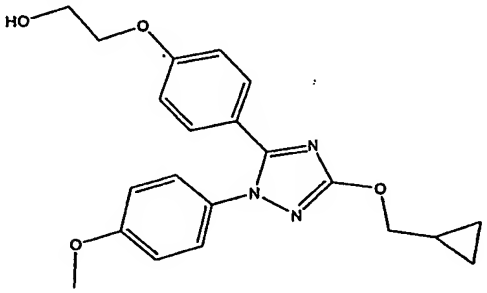
1H NMR (CDCl3, ppm) d 1.51-2.09(8H, m), 2.21(1H, t, J=6.2 Hz), 3.84(3H, s), 3.89-4.01(2H, m), 4.02-4.15(2H, m), 5.15-5.30(1H, m), 6.75-6.97(4H, m), 7.20-7.35(2H, m), 7.37-7.49(2H, m),
MS (ESI, m/e) 396(M+1)

Example 180

The following compound was obtained in substantially the same manner as that of Example 113.

E180

2-{4-[3-(cyclopropylmethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}-ethanol



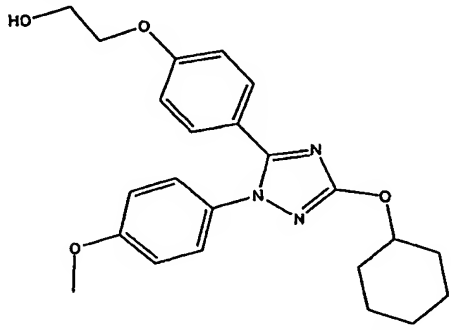
1H NMR (CDCl3, ppm) d 0.33-0.45(2H, m), 0.55-0.69(2H, m), 1.22-1.45(1H, m), 2.19(1H, t, J=6.1 Hz), 3.84(3H, s), 3.89-4.02(2H, m), 4.03-4.13(2H, m), 4.16(2H, d, J=7.2 Hz), 6.75-6.99(4H, m), 7.18-7.32(2H, m), 7.36-7.50(2H, m),
MS (ESI, m/e) 382(M+1)

Example 181

The following compound was obtained in substantially the same manner as that of Example 113.

E181

2-{4-[3-(cyclohexyloxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}-ethanol



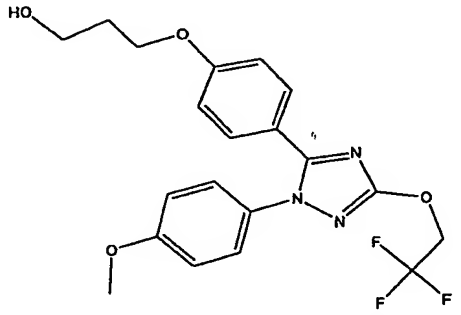
1H NMR (CDCl3, ppm) d 1.19-2.19(9H, m), 3.84(3H, s), 3.89-4.02(2H, m), 4.02-4.13(2H, m), 4.77(1H, 5th, J=4.1 Hz), 6.77-6.98(4H, m), 7.20-7.34(2H, m), 7.36-7.49(2H, m),
MS (ESI, m/e) 410(M+1)

Example 182

The following compound was obtained in substantially the same manner as that of Example 113.

E182

3-{4-[1-(4-methoxyphenyl)-3-(2,2,2-trifluoroethoxy)-1H-1,2,4-triazol-5-yl]phenoxy}-1-propanol



1H NMR (CDCl3, ppm) d 1.82-2.23(3H, m), 3.85(3H, s), 4.01-4.18(2H, m), 4.19-4.40(2H, m), 4.74(2H, q, J=8.2 Hz), 6.77-6.88(2H, m), 6.89-7.00(2H, m), 7.20-7.35(2H, m), 7.36-7.50(2H, m),
MS (ESI, m/e) 424(M+1)

Example 183

The following compound was obtained in substantially the same manner as that of Example 113.

E183

2-{4-[3-isobutoxy-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethanol

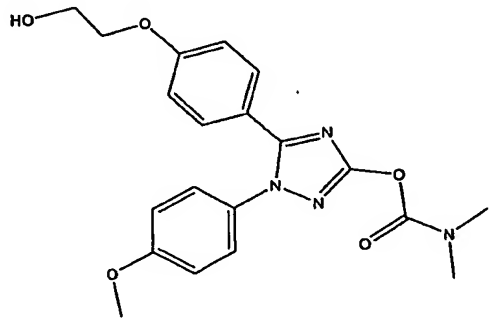
1H NMR (CDCl3, ppm) d 1.04(6H, d, J=6.7 Hz), 1.96-2.07(1H, m), 2.07-2.29(1H, m), 3.84(3H, s), 3.90-4.02(2H, m), 4.02-4.18(4H, m), 6.76-7.00(4H, m), 7.19-7.34(2H, m), 7.35-7.49(2H, m),
MS (ESI, m/e) 384(M+1)

Example 184

The following compound was obtained in substantially the same manner as that of Example 113.

E184

5-[4-(2-hydroxyethoxy)phenyl]-1-(4-methoxyphenyl)-1H-1,2,4-triazol-3-yl dimethylcarbamate



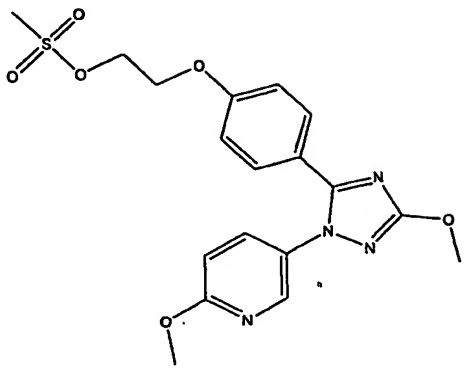
1H NMR (CDCl3, ppm) d 2.18(1H, bt, J=5.9 Hz), 3.03(3H, s), 3.13(3H, s), 3.85(3H, s), 3.88-4.25(4H, m), 6.71-7.01(4H, m), 7.22-7.39(2H, m), 7.40-7.57(2H, m),
MS (ESI, m/e) 399(M+1)

Example 185

The following compound was obtained in substantially the same manner as that of Example 124.

E185

2-{4-[3-methoxy-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl methanesulfonate



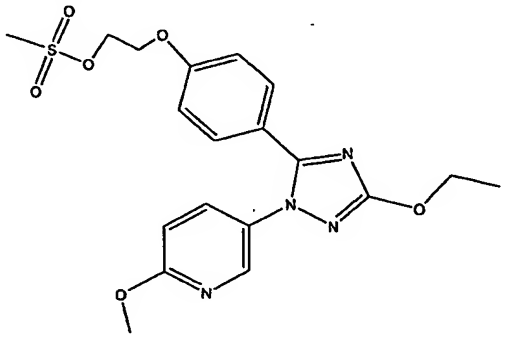
MS (ESI, m/e) 421(M+1)

Example 186

The following compound was obtained in substantially the same manner as that of Example 124.

E186

2-{4-[3-ethoxy-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl methanesulfonate



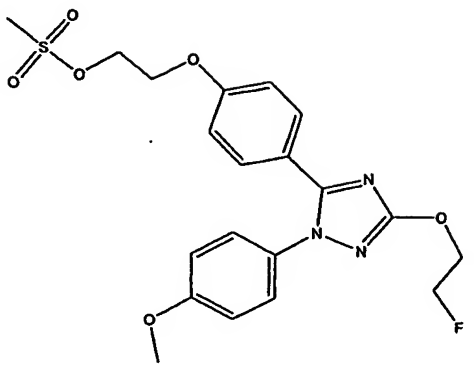
MS (ESI, m/e) 435(M+1)

Example 187

The following compound was obtained in substantially the same manner as that of Example 124.

E187

2-{4-[3-(2-fluoroethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl methanesulfonate



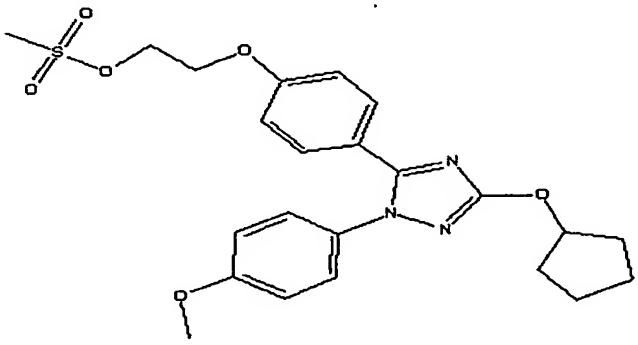
MS (ESI, m/e) 452(M+1)

Example 188

The following compound was obtained in substantially the same manner as that of Example 124.

E188

2-{4-[3-(cyclopentyloxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl methanesulfonate



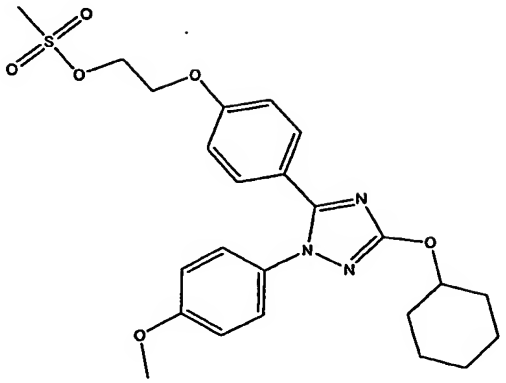
MS (ESI, m/e) 474(M+1)

Example 189

The following compound was obtained in substantially the same manner as that of Example 124.

E189

2-{4-[3-(cyclohexyloxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl methanesulfonate



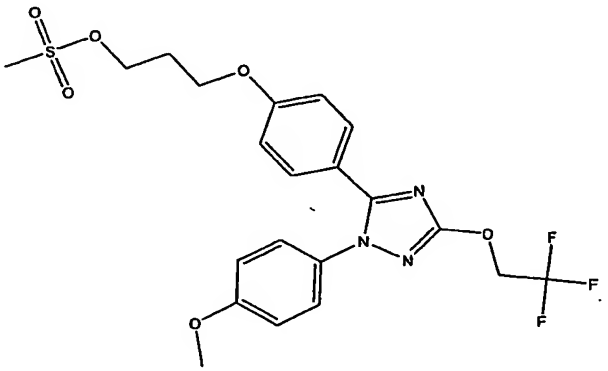
MS (ESI, m/e) 488(M+1)

Example 190

The following compound was obtained in substantially the same manner as that of Example 124.

E190

3-{4-[1-(4-methoxyphenyl)-3-(2,2,2-trifluoroethoxy)-1H-1,2,4-triazol-5-yl]phenoxy}propyl methanesulfonate



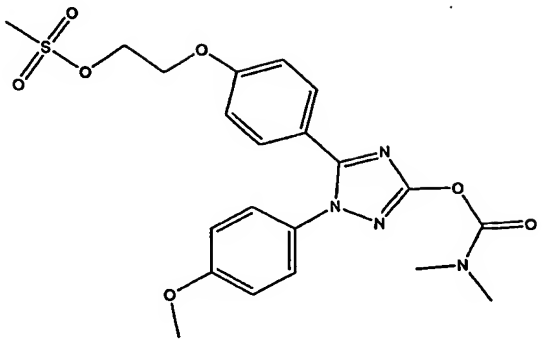
MS (ESI, m/e) 502(M+1)

Example 191

The following compound was obtained in substantially the same manner as that of Example 124.

E191

2-{4-[3-{[(dimethylamino)carbonyl]oxy}-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}-ethyl methanesulfonate



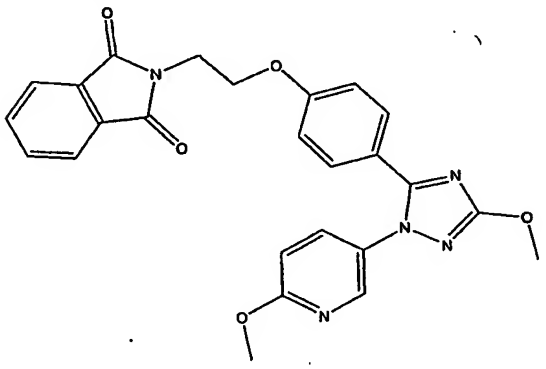
MS (ESI, m/e) 477(M+1)

Example 192

The following compound was obtained in substantially the same manner as that of Example 125.

E192

2-(2-{4-[3-methoxy-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione



1H NMR (CDCl3, ppm) d 3.95(3H, s), 4.04(3H, s), 4.07-4.17(2H, m), 4.17-4.29(2H, m), 6.71-6.90(3H, m), 7.32-7.45(2H, m), 7.38(1H, dd, J=6.7,2.0 Hz), 7.69-7.80(2H, m), 7.80-7.93(2H, m), 8.12(1H, d, J=2.4 Hz),

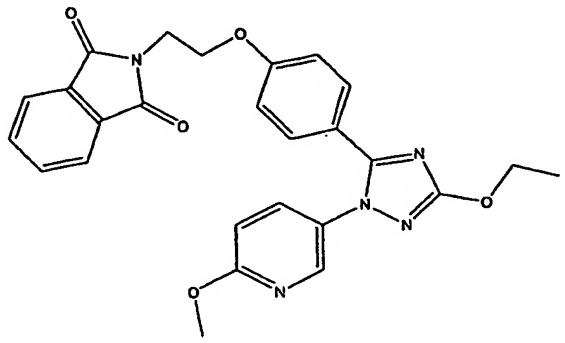
MS (ESI, m/e) 472(M+1)

Example 193

The following compound was obtained in substantially the same manner as that of Example 125.

E193

2-(2-{4-[3-ethoxy-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione



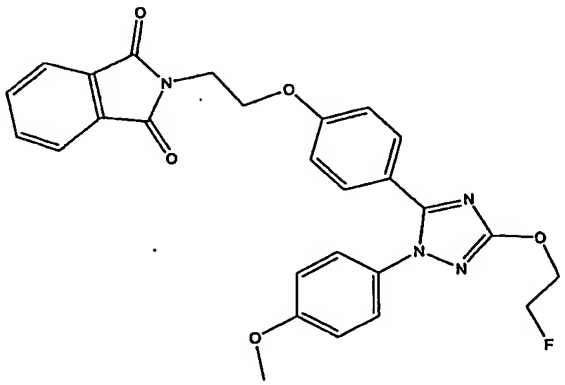
1H NMR (CDCl3, ppm) d 1.45(3H, t, J=7.0 Hz), 3.95(3H, s), 4.05-4.18(2H, m), 4.18-4.30(2H, m), 4.38(2H, q, J=7.0 Hz), 6.71-6.89(3H, m), 7.30-7.45(2H, m), 7.54(1H, dd, J=8.8,2.6 Hz), 7.67-7.80(2H, m), 7.80-7.92(2H, m), 8.12(1H, d, J=3.0 Hz), MS (ESI, m/e) 486(M+1)

Example 194

The following compound was obtained in substantially the same manner as that of Example 125.

E194

2-(2-{4-[3-(2-fluoroethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}-ethyl)-1H-isoindole-1,3(2H)-dione



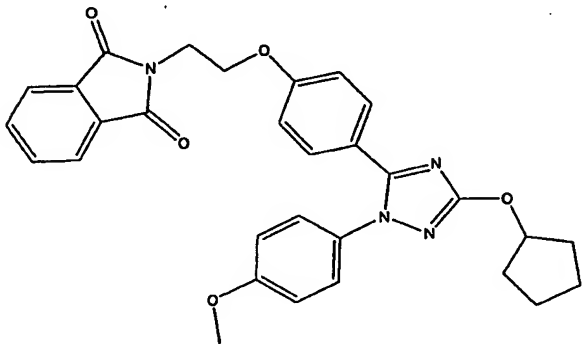
1H NMR (CDCl3, ppm) d 3.84(3H, s), 4.05-4.15(2H, m), 4.15-4.28(2H, m), 4.47-4.58(1H, m), 4.59-4.70(2H, m), 4.82-4.94(1H, m), 6.72-6.85(2H, m), 6.85-6.95(2H, m), 7.16-7.30(2H, m), 7.31-7.45(2H, m), 7.69-7.79(2H, m), 7.80-7.95(2H, m), MS (ESI, m/e) 503(M+1)

Example 195

The following compound was obtained in substantially the same manner as that of Example 125.

E195

2-(2-{4-[3-(cyclopentyloxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}-ethyl)-1H-isoindole-1,3(2H)-dione



1H NMR (CDCl3, ppm) d 1.51-2.06(8H, m), 3.83(3H, s), 4.05-4.15(2H, m), 4.16-4.28(2H, m), 5.25-5.29(1H, m), 6.74-6.86(2H, m), 6.86-6.98(2H, m), 7.19-7.32(2H, m), 7.32-7.45(2H, m), 7.68-7.80(2H, m), 7.80-7.94(2H, m),

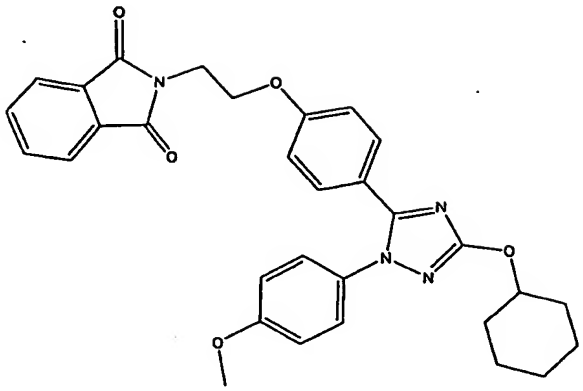
MS (ESI, m/e) 525(M+1)

Example 196

The following compound was obtained in substantially the same manner as that of Example 125.

E196

2-(2-{4-[3-(cyclohexyloxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}-ethyl)-1H-isoindole-1,3(2H)-dione



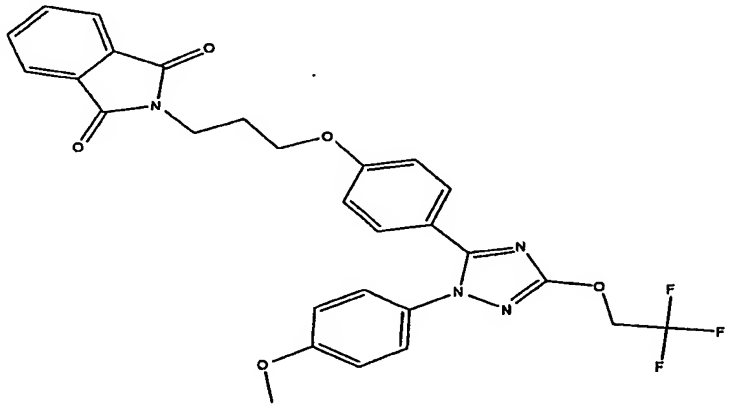
MS (ESI, m/e) 539(M+1)

Example 197

The following compound was obtained in substantially the same manner as that of Example 125.

E197

2-(3-{4-[1-(4-methoxyphenyl)-3-(2,2,2-trifluoroethoxy)-1H-1,2,4-triazol-5-yl]-phenoxy}propyl)-1H-isoindole-1,3(2H)-dione



1H NMR (DMSO-d6, ppm) d 1.91-2.17(2H, m), 3.74(2H, t, J=6.7 Hz), 3.81(3H, s), 3.95-4.11(2H, m), 4.99(2H, q, J=8.8 Hz), 6.81(2H, d, J=8.9 Hz), 7.00-7.11(2H, m), 7.25-7.45(4H, m), 7.77-7.92(4H, m),

MS (ESI, m/e) 553(M+1)

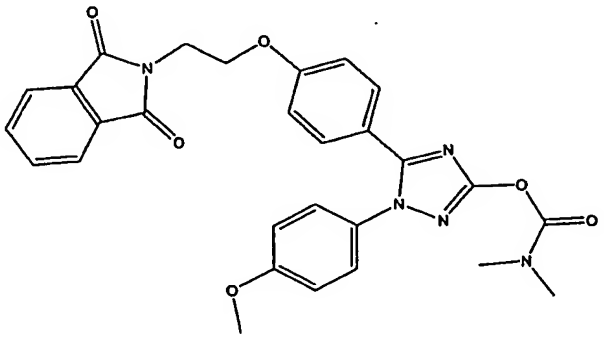
Example 198

The following compound was obtained in substantially the same

manner as that of Example 125.

E198

5-{4-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethoxy]-phenyl}-1-(4-methoxyphenyl)-1H-1,2,4-triazol-3-yl dimethylcarbamate



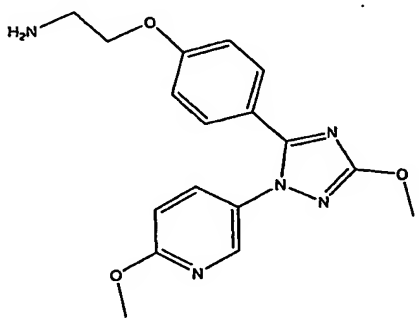
1H NMR (DMSO-d6, ppm) d 2.94(3H, s), 3.06(3H, s), 3.81(3H, s), 3.96(2H, bt, J=5.2 Hz), 4.23(2H, bt, J=5.4 Hz), 6.85-6.98(2H, m), 6.99-7.11(2H, m), 7.25-7.41(4H, m), 7.78-7.95(4H, m), MS (ESI, m/e) 528(M+1)

Example 199

The following compound was obtained in substantially the same manner as that of Example 126.

E199

2-{4-[3-methoxy-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethylamine



1H NMR (CDCl3, ppm) d 3.09(2H, t, J=5.2 Hz), 3.90-4.06(8H, m), 6.73-6.92(3H, m), 7.37-7.48(2H, m), 7.58(1H, dd, J=8.9,2.6 Hz), 8.15(1H, d, J=2.4 Hz),

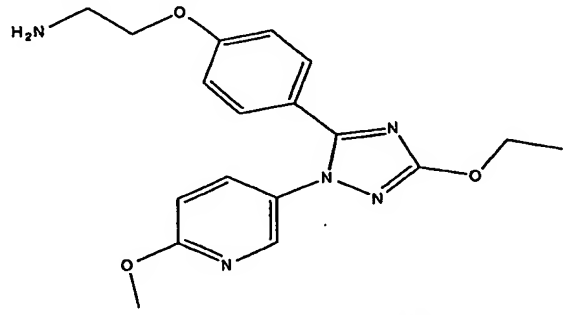
MS (ESI, m/e) 342(M+1)

Example 200

The following compound was obtained in substantially the same manner as that of Example 126.

E200

2-{4-[3-ethoxy-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethanamine



1H NMR (CDCl3, ppm) d 1.46(3H, t, J=7.0 Hz), 3.08(2H, t, J=5.2 Hz), 3.91-4.06(5H, m), 4.39(2H, q, J=7.0 Hz), 6.74-6.92(3H, m), 7.37-7.49(2H, m), 7.57(1H, dd, J=8.8,2.6 Hz), 8.15(1H, d, J=2.4 Hz),

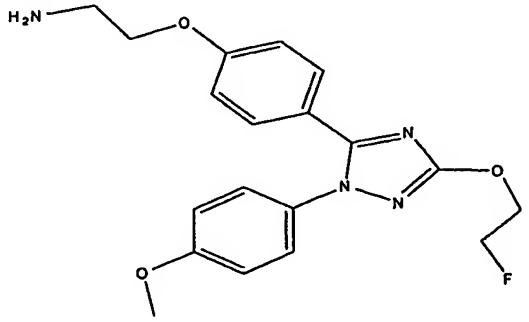
MS (ESI, m/e) 356(M+1)

Example 201

The following compound was obtained in substantially the same manner as that of Example 126.

E201

2-{4-[3-(2-fluoroethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethylamine



1H NMR (CDCl3, ppm) d 3.08(2H, t, J=5.1 Hz), 3.85(3H, s), 3.98(2H, t, J=5.1 Hz), 4.47-4.59(1H, m), 4.50-4.70(2H, m), 4.82-4.95(1H, m), 6.78-6.89(2H, m), 6.89-6.99(2H, m), 7.19-7.35(2H, m), 7.36-7.49(2H, m),

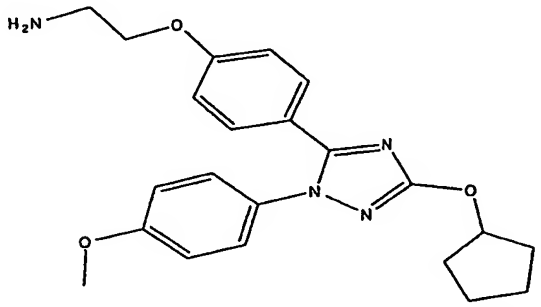
MS (ESI, m/e) 373(M+1)

Example 202

The following compound was obtained in substantially the same manner as that of Example 126.

E202

2-{4-[3-(cyclopentyloxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethylamine



1H NMR (CDCl3, ppm) d 1.47-2.08(10H, m), 3.07(2H, t, J=5.2 Hz), 3.84(3H, s), 3.98(2H, t, J=5.1 Hz), 5.18-5.31(1H, m), 6.77-6.89(2H, m), 6.89-6.99(2H, m), 7.21-7.34(2H, m), 7.35-7.49(2H, m),

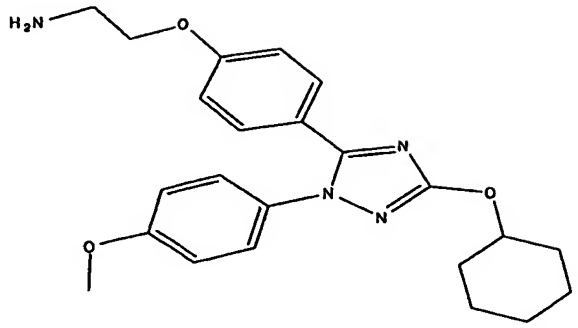
MS (ESI, m/e) 395(M+1)

Example 203

The following compound was obtained in substantially the same manner as that of Example 126.

E203

2-{4-[3-(cyclohexyloxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethanamine



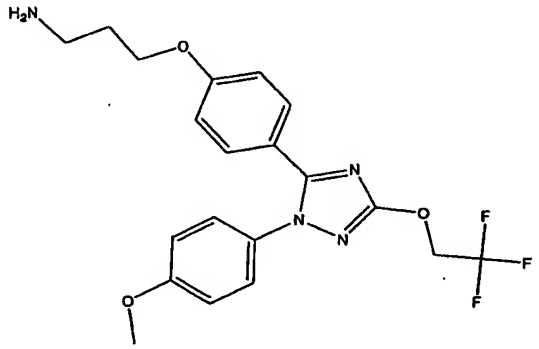
1H NMR (DMSO-d6, ppm) d 1.21-2.12(12H, m), 2.84(2H, t, J=5.8 Hz), 3.80(3H, s), 3.91(2H, t, J=5.7 Hz), 4.58-4.77(1H, m), 6.87-6.97(2H, m), 6.97-7.10(2H, m), 7.25-7.41(4H, m),
MS (ESI, m/e) 409(M+1)

Example 204

The following compound was obtained in substantially the same manner as that of Example 126.

E204

3-{4-[1-(4-methoxyphenyl)-3-(2,2,2-trifluoroethoxy)-1H-1,2,4-triazol-5-yl]phenoxy}-1-propanamine



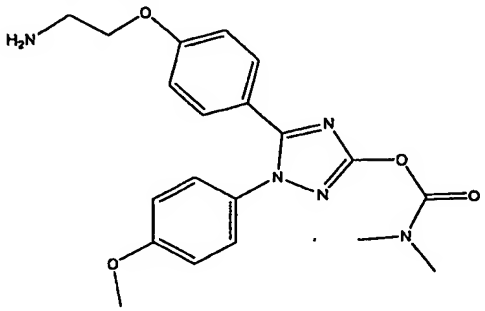
1H NMR (CDCl3, ppm) d 1.92(2H, 5th, J=6.4 Hz), 2.90(2H, t, J=6.7 Hz), 3.85(3H, s), 4.05(2H, t, J=6.1 Hz), 4.74(2H, q, J=8.3 Hz), 6.76-6.89(2H, m), 6.89-7.02(2H, m), 7.19-7.35(2H, m), 7.35-7.49(2H, m),
MS (ESI, m/e) 423(M+1)

Example 205

The following compound was obtained in substantially the same manner as that of Example 126.

E205

5-[4-(2-aminoethoxy)phenyl]-1-(4-methoxyphenyl)-1H-1,2,4-triazol-3-yl dimethylcarbamate

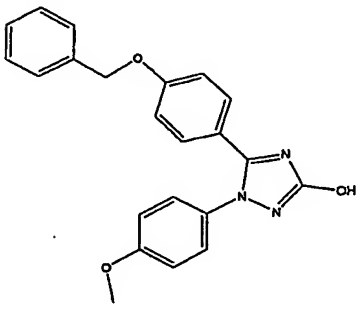


1H NMR (CDCl3, ppm) d 3.03(3H, s), 3.14(3H, s), 3.03-3.13(2H, m), 3.85(3H, s), 3.99(2H, t, J=5.1 Hz), 6.77-6.99(4H, m), 7.18-7.36(2H, m), 7.37-7.50(2H, m),
MS (ESI, m/e) 398(M+1)

Preparation 135

Under ice-bath cooling, diethyl azodicarboxylate (DEAD, 805 mg, 8.03 mmol) was added to a suspension of P135-1 (2 g, 5.36 mmol) and triphenylphosphine (2.11 g, 8.03 mmol) in 20 ml of THF. The mixture was stirred for 15 hours at room temperature under nitrogen atmosphere. The solvent was removed under reduced pressure. The residue was purified by silicagel column chromatography to give P135 (2.05 g, 84% yield).

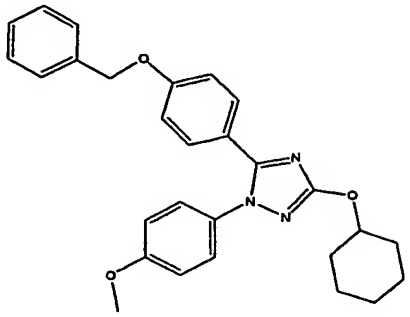
P135-1



P135

5-[4-(benzyloxy)phenyl]-3-(cyclohexyloxy)-1-(4-

methoxyphenyl)-1H-1,2,4-triazole



1H NMR (CDCl3, ppm) d 1.30-2.19(10H, m), 3.84(3H, s), 4.77(1H, 7th, J=3.9 Hz), 5.05(2H, s), 6.82-6.97(4H, m), 7.20-7.49(9H, m),

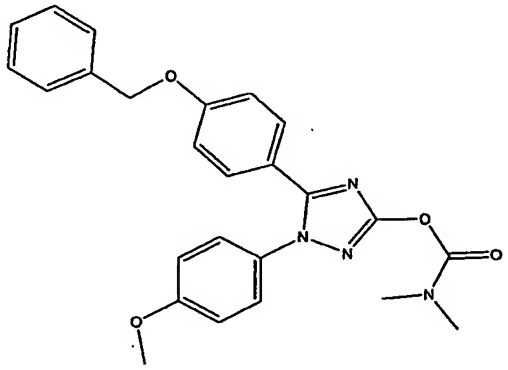
MS (ESI, m/e) 456(M+1)

Preparation 136

The following compound was obtained in substantially the same manner as that of Preparation 139.

P136

5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-1H-1,2,4-triazol-3-yl dimethylcarbamate



1H NMR (DMSO-d6, ppm) d 2.94(3H, s), 3.07(3H, s), 3.82(3H, s), 5.11(2H, s), 6.98-7.12(4H, m), 7.29-7.51(9H, m),

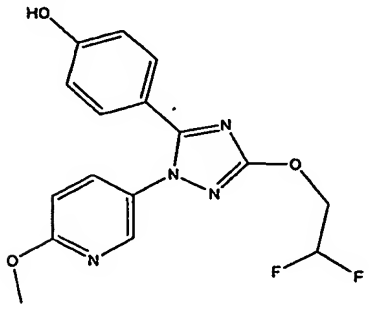
MS (ESI, m/e) 445(M+1)

Preparation 137

The following compound was obtained in substantially the same manner as that of Preparation 60.

P137

4-[3-(2,2-difluoroethoxy)-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenol



1H NMR (DMSO-d6, ppm) d 3.90(3H, s), 4.57(2H, td, J=14.9,3.4 Hz), 6.44(1H, tt, J=54.3,3.3 Hz), 6.70-6.83(1H, m), 6.96(1H, d, J=9.0 Hz), 7.20-7.35(2H, m), 7.79(1H, dd, J=8.8,2.7 Hz), 8.22(1H, d, J=2.7 Hz), 10.1(1H, bs),

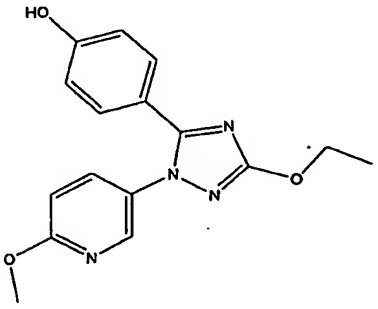
MS (ESI, m/e) 349(M+1)

Preparation 138

The following compound was obtained in substantially the same manner as that of Preparation 43.

P138

4-[3-ethoxy-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenol



1H NMR (CDCl3, ppm) d 1.35(3H, t, J=7.0 Hz), 3.89(3H, s), 4.29(2H, q, J=7.0 Hz), 6.70-6.81(2H, m), 6.94(1H, d, J=9.0 Hz), 7.20-7.32(2H, m), 7.76(1H, dd, J=8.8,2.8 Hz), 8.19(1H, d, J=2.4 Hz), 10.0(1H, bs),

MS (ESI, m/e) 313(M+1)

Preparation 139

Dimethylcarbamic chloride was added to a mixture of 1,5-bis(4-methoxyphenyl)-1H-1,2,4-triazol-3-ol (200 mg, 0.673 mmol) and pyridine (0.114 ml, 1.41 mmol) in dichloromethane (5 ml). Then the solution was stirred at 45°C for 17 hours. Water and ethyl acetate were poured into the mixture and the organic layer was separated, washed with water and brine, and dried over magnesium sulfate. The solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane - ethyl acetate 1:2). The desired product was washed with isopropyl ether to give 1,5-bis(4-methoxyphenyl)-1H-1,2,4-triazol-3-yl dimethylcarbamate.(88 mg, 35.5% yield)

1H NMR (CDCl3, ppm) δ 3.03(3H, s), 3.14(3H, s), 3.81(3H, s), 3.85(3H, s), 6.75-6.99(4H, m), 7.20-7.38(2H, m), 7.39-7.52(2H, m),

MS (ESI, m/e) 369(M+1)

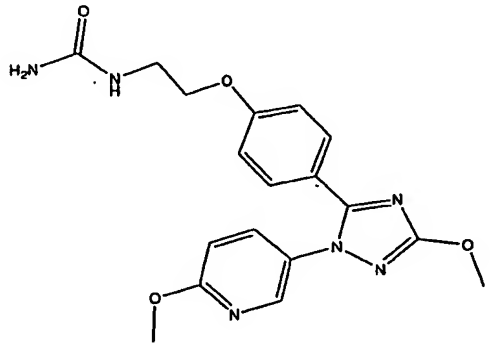
mp 121-123 °C

Example 206

The following compound was obtained in substantially the same manner as that of Example 127.

E206

N-(2-{4-[3-methoxy-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea



1H NMR (DMSO-d6, ppm) d 3.25-3.49(2H, m), 3.89(3H, s), 3.94(3H, s), 3.90-4.05(2H, m), 5.52(2H, s), 6.15(1H, bt, J=5.6 Hz), 6.91-7.08(3H, m), 7.29-7.45(2H, m), 7.79(1H, dd, J=8.8,2.6 Hz),

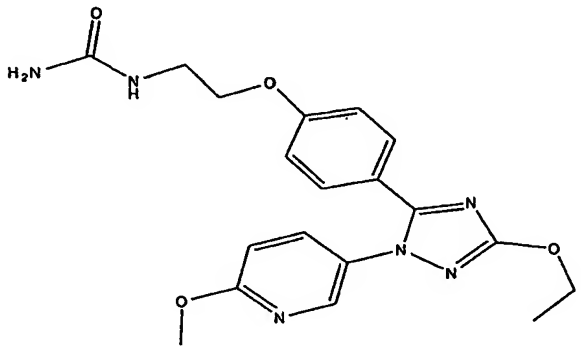
8.22(1H, d, J=2.5 Hz),
MS (ESI, m/e) 385(M+1)

Example 207

The following compound was obtained in substantially the same manner as that of Example 127.

E207

N-(2-{4-[3-ethoxy-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea



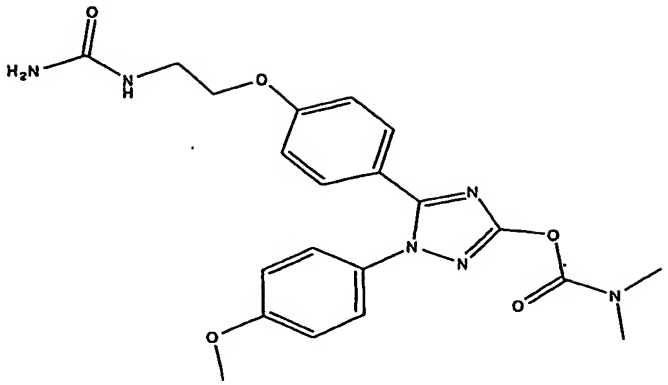
1H NMR (DMSO-d6, ppm) d 1.36(3H, t, J=7.0 Hz), 3.25-3.49(2H, m), 3.89(3H, s), 3.96(2H, t, J=5.6 Hz), 4.31(2H, q, J=7.0 Hz), 5.52(2H, s), 6.15(1H, bt, J=5.5 Hz), 6.90-7.02(3H, m), 7.36(2H, bd, J=8.8 Hz), 7.78(1H, dd, J=8.8,2.6 Hz), 8.21(1H, d, J=2.6 Hz),
MS (ESI, m/e) 398(M+1)

Example 208

The following compound was obtained in substantially the same manner as that of Example 127.

E208

5-(4-{2-[(aminocarbonyl)amino]ethoxy}phenyl)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-3-yl dimethylcarbamate



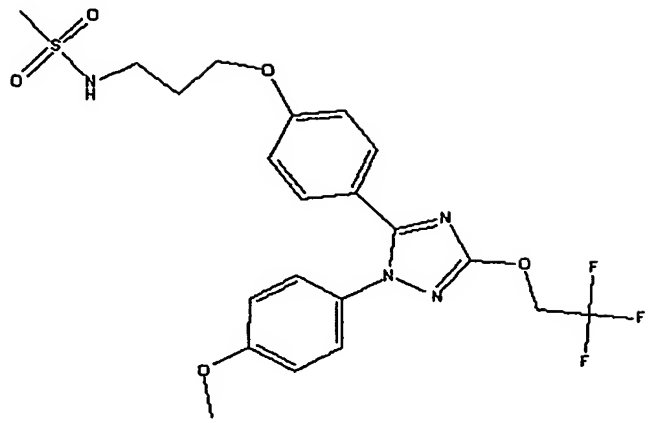
1H NMR (CDCl3, ppm) d 3.03(3H, s), 3.14(3H, s), 3.51-3.60(2H, m), 3.84(3H, s), 3.95-4.03(2H, m), 4.56(2H, bs), 5.25-5.38(1H, m), 6.72-6.80(2H, m), 6.87-6.95(2H, m), 7.22-7.31(2H, m), 7.36-7.45(2H, m),
MS (ESI, m/e) 441(M+1)

Example 209

Under ice-bath-cooling, a mixture of E204 (100 mg, 0.237 mmol), pyridine (28 mg, 0.355 mmol) and methanesulfonyl chloride (41 mg, 0.355 mmol) in dichloromethane (1 ml) was stirred for 4 hours. Water and ethyl acetate were added to the mixture and the organic layer was separated, washed with 0.1 N hydrochloric acid, water and brine, and dried over magnesium sulfate. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give E209 (30 mg, 25 % yield).

E209

N-(3-{4-[1-(4-methoxyphenyl)-3-(2,2,2-trifluoroethoxy)-1H-1,2,4-triazol-5-yl]-phenoxy}propyl)methanesulfonamide



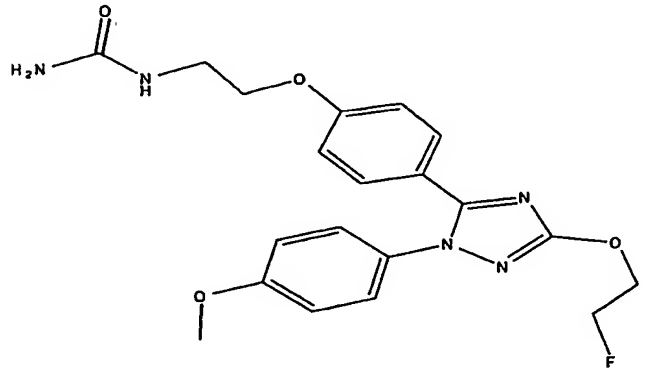
1H NMR (DMSO-d6, ppm) d 1.89(2H, 5th, J=6.4 Hz), 2.88(3H, s), 3.03-3.18(2H, m), 3.81(3H, s), 4.03(2H, bt, J=6.1 Hz), 4.99(2H, q, J=8.9 Hz), 6.89-7.15(5H, m), 7.29-7.48(4H, m),
MS (ESI, m/e) 501(M+1)

Example 210

The following compound was obtained in substantially the same manner as that of Example 82.

E210

N-(2-{4-[3-(2-fluoroethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea



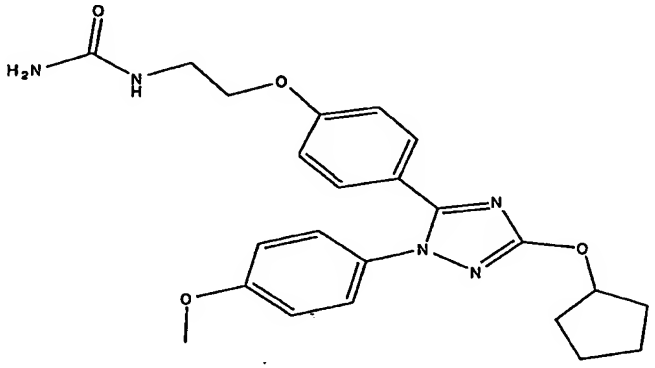
1H NMR (DMSO-d6, ppm) d 3.20-3.50(2H, m), 3.80(3H, s), 3.95(2H, t, J=5.5 Hz), 4.38-4.49(1H, m), 4.51-4.70(4H, m), 4.81-4.95(2H, m), 5.53(2H, bs), 6.12(1H, bt), 6.89-7.11(4H, m), 7.25-7.41(4H, m),
MS (ESI, m/e) 416(M+1)

Example 211

The following compound was obtained in substantially the same manner as that of Example 82.

E211

N-(2-{4-[3-(cyclopentyloxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea



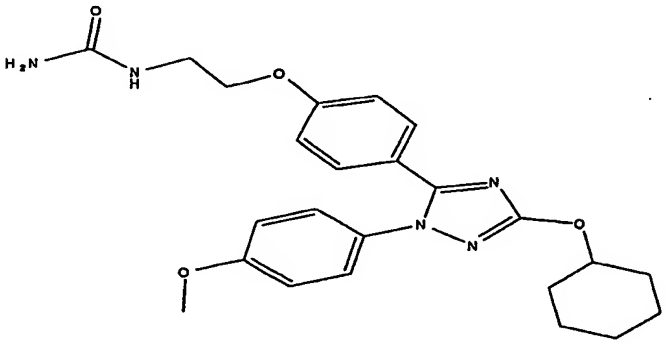
1H NMR (DMSO-d6, ppm) d 1.21-2.12(12H, m), 2.84(2H, t, J=5.8 Hz), 3.80(3H, s), 3.91(2H, t, J=5.7 Hz), 4.58-4.77(1H, m), 6.87-6.97(2H, m), 6.97-7.10(2H, m), 7.25-7.41(4H, m),
MS (ESI, m/e) 438(M+1)

Example 212

The following compound was obtained in substantially the same manner as that of Example 82.

E212

N-(2-{4-[3-(cyclohexyloxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea



1H NMR (DMSO-d6, ppm) d 1.25-2.12(10H, m), 3.25-3.39(2H, m), 3.80(3H, s), 3.95(2H, t, J=5.7 Hz), 4.58-4.75(1H, m), 5.52(2H, s), 6.15(1H, bt, J=5.7 Hz), 6.89-7.07(4H, m), 7.25-7.39(4H, m), MS (ESI, m/e) 452(M+1)

Example 213

The following compound was obtained in substantially the same manner as that of Example 82.

E213

N-(3-{4-[1-(4-methoxyphenyl)-3-(2,2,2-trifluoroethoxy)-1H-1,2,4-triazol-5-yl]phenoxy}propyl)urea

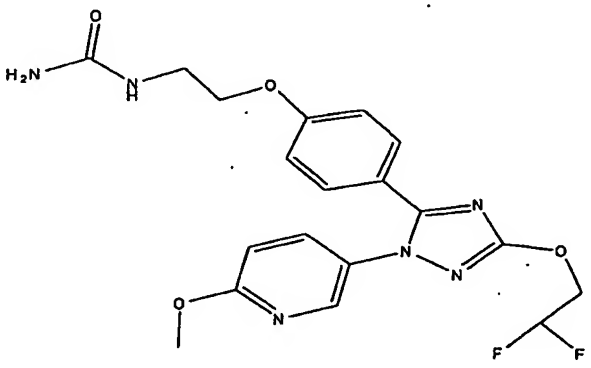
1H NMR (DMSO-d6, ppm) d 1.79(2H, 5th, J=6.4 Hz), 3.02-3.18(2H, m), 3.81(3H, s), 3.98(2H, bt, J=6.2 Hz), 4.99(2H, q, J=8.8 Hz), 5.40(2H, bs), 6.01(1H, bt, J=5.7 Hz), 6.89-7.12(4H, m), 7.29-7.47(4H, m),
MS (ESI, m/e) 466(M+1)

Example 214

The following compound was obtained in substantially the same manner as that of Example 77.

E214

N-(2-{4-[3-(2,2-difluoroethoxy)-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea



1H NMR (DMSO-d6, ppm) d 3.22-3.40(5H, m), 3.90(3H, s), 3.96(2H, t, J=5.6 Hz), 4.58(2H, td, J=14.9,3.3 Hz), 5.53(2H, bs),

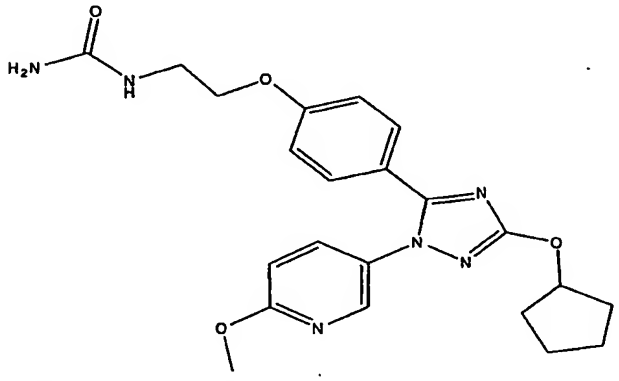
6.10-6.22(1H, m), 6.44(1H, tt, J=54.2,3.4 Hz), 6.90-7.08(3H, m), 7.38(2H, d, J=8.8 Hz), 7.80(1H, dd, J=8.8,2.8 Hz), 8.24(1H, d, J=2.5 Hz),
MS (ESI, m/e) 435(M+1)

Example 215

The following compound was obtained in substantially the same manner as that of Example 77.

E215

N-(2-{4-[3-(cyclopentyloxy)-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea



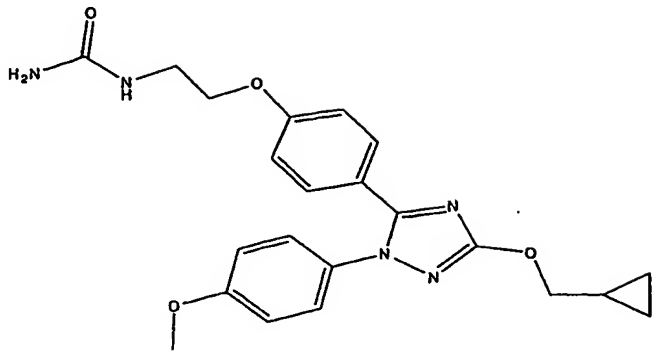
1H NMR (DMSO-d6, ppm) d 1.52-1.98(8H, m), 3.25-3.40(2H, m), 3.89(3H, s), 3.96(2H, bt, J=5.5 Hz), 5.07-5.20(1H, m), 5.53(2H, bs), 6.16(1H, bt, J=5.7 Hz), 6.90-7.05(3H, m), 7.36(2H, d, J=8.7 Hz), 7.77(1H, dd, J=8.8,2.6 Hz), 8.21(1H, d, J=2.6 Hz),
MS (ESI, m/e) 439(M+1)

Example 216

The following compound was obtained in substantially the same manner as that of Example 77.

E216

N-(2-{4-[3-(cyclopropylmethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]-phenoxy}ethyl)urea



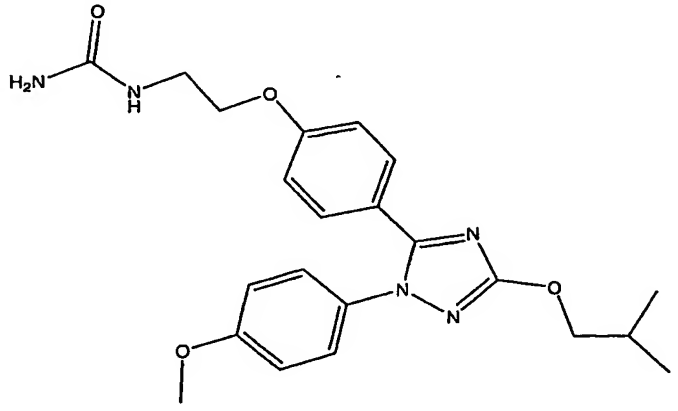
1H NMR (DMSO-d6, ppm) d 0.30-0.44(2H, m), 0.50-0.65(2H, m), 1.17-1.40(1H, m), 3.22-3.40(2H, m), 3.80(3H, s), 3.95(2H, t, J=5.6 Hz), 4.07(2H, d, J=7.2 Hz), 5.52(2H, bs), 6.15(1H, bt, J=5.7 Hz), 6.89-7.10(4H, m), 7.25-7.44(4H, m),
MS (ESI, m/e) 424(M+1)

Example 217

The following compound was obtained in substantially the same manner as that of Example 77.

E217

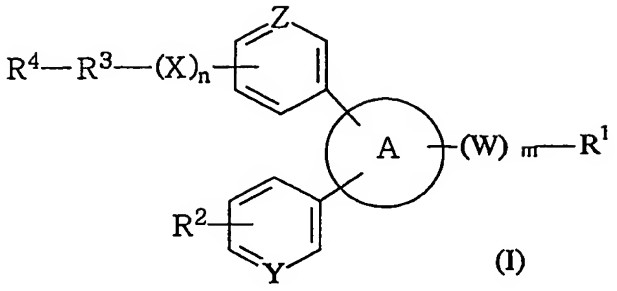
N-(2-{4-[3-isobutoxy-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea



1H NMR (DMSO-d6, ppm) d 0.98(6H, d, J=6.8 Hz), 1.95-2.20(1H, m), 3.23-3.39(2H, m), 3.80(3H, s), 3.95(2H, t, J=5.6 Hz), 4.02(2H, d, J=6.5 Hz), 5.53(2H, bs), 6.15(1H, bt, J=5.6 Hz), 6.88-7.11(4H, m), 7.26-7.45(4H, m),
MS (ESI, m/e) 426(M+1)

CLAIMS

1. A compound of the formula (I):



(I)

wherein R^1 is lower alkyl optionally substituted with suitable substituent(s); cyclo(lower)alkyl; lower alkynyl; cyano; acyl; heterocyclic group; lower alkenyl; lower alkoxy optionally substituted with lower alkoxy, N,N-di(lower)alkylcarbamoyl, cyclo(lower)alkyl, aroyl or halogen; or cyclo(lower)alkyloxy;

R^2 is lower alkyl, lower alkoxy, cyano or 1H-pyrrol-1-yl;

R^3 is lower alkylene or lower alkenylene;

R^4 is hydroxy, protected hydroxy, amino, protected amino, acylamino, acyl, cyano or heterocyclic group;

X is O, S, SO or SO_2;

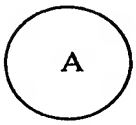
Y is CH or N;

Z is CH or N;

W is O, S, SO or SO_2;

m is 0 or 1;

n is 0 or 1; and



is triazole or imidazole;

or salts thereof.

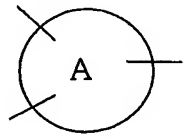
2. The compound of Claim 1, wherein

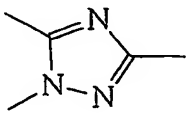
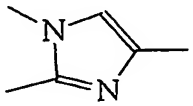
R^1 is lower alkyl optionally substituted with suitable

substituent(s); cyclo(lower)alkyl; lower alkynyl; cyano; acyl; or heterocyclic group;

R^4 is hydroxy, protected hydroxy, amino, protected amino, acylamino, acyl or cyano;

Z is CH; and



is  or  .

3. The compound of Claim 2, wherein

R^1 is lower alkyl optionally substituted with one or more halogen atom(s); cyclo(lower)alky; lower alkanoyl; carbamoyl substituted with lower alkyl; cyclo(lower)alkylcarbonyl; aroyl; or heterocycliccarbonyl;

R^2 is lower alkoxy;

X is O; and

W is O.

4. The compound of Claim 3, wherein

R3 is lower alkylene; and

R4 is hydroxy, amino, carbamoylamino, lower alkylsulfonylamino, lower alkanoylamino, sulfamoylamino or lower alkylsulfonyl.

5. The compound of Claim 4, which is

2-{4-[2-(4-methoxyphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl}ethanol,

N,N-diethyl-1-[4-(2-hydroxyethoxy)phenyl]-2-(4-methoxyphenyl)-1H-imidazole-4-carboxamide,

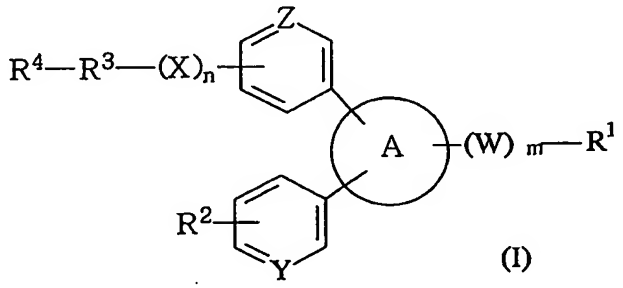
cyclopentyl[1-[4-(2-hydroxyethoxy)phenyl]-2-(6-methoxy-3-pyridinyl)-1H-imidazol-4-yl]methanone,

2-{4-[2-(4-methoxyphenyl)-4-(1-piperidinylcarbonyl)-1H-imidazol-1-yl]phenoxy}ethanol,

1-[1-[4-(2-hydroxyethoxy)phenyl]-2-(4-methoxyphenyl)-1H-imidazol-4-yl]-2-methyl-1-propanone,

(2-{4-[3-methoxy-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)amine,
(2-{4-[1-(4-methoxyphenyl)-3-(2,2,2-trifluoroethoxy)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)amine,
2-{4-[3-isopropoxy-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethanol,
2-{4-[1-(4-methoxyphenyl)-3-(2,2,2-trifluoroethoxy)-1H-1,2,4-triazol-5-yl]phenoxy}ethanol,
N-(2-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea,
N-(2-{4-[3-isopropoxy-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea,
N-(2-{4-[3-methoxy-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea,
N-(2-{4-[1-(4-methoxyphenyl)-3-(2,2,2-trifluoroethoxy)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea,
N-(2-{4-[1-(6-methoxy-3-pyridinyl)-3-(2,2,2-trifluoroethoxy)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea,
N-(2-{4-[3-(2,2-difluoroethoxy)-1-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea, or
N-(2-{4-[3-(cyclopentyloxy)-1-(6-methoxy-3-pyridinyl)-1H-1,2,4-triazol-5-yl]phenoxy}ethyl)urea.

6. A process of preparing a compound of the formula:



(I)

wherein R^1 is lower alkyl optionally substituted with suitable substituent(s); cyclo(lower)alkyl; lower alkynyl; cyano; acyl; heterocyclic group; lower

alkenyl; lower alkoxy optionally substituted with lower alkoxy, N,N-di(lower)alkylcarbamoyl, cyclo(lower)alkyl, aroyl or halogen; or cyclo(lower)alkyloxy;

R^2 is lower alkyl, lower alkoxy, cyano or 1H-pyrrol-1-yl;

R^3 is lower alkylene or lower alkenylene;

R^4 is hydroxy, protected hydroxy, amino, protected amino, acylamino, acyl, cyano or heterocyclic group;

X is O, S, SO or SO_2;

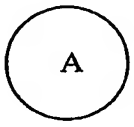
Y is CH or N;

Z is CH or N;

W is O, S, SO or SO_2;

m is 0 or 1;

n is 0 or 1; and

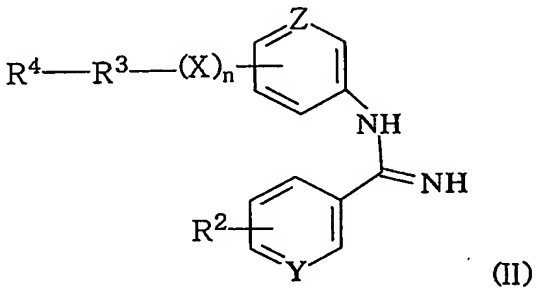


is triazole or imidazole;

or salts thereof,

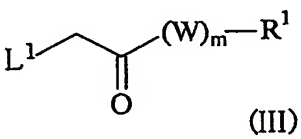
Which comprises,

1) reacting a compound of the formula:



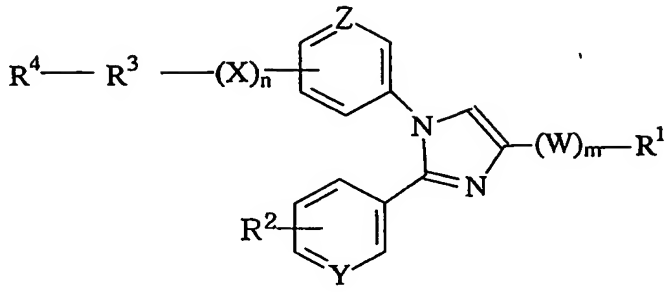
(II)

or its salt with a compound of the formula:



(III)

or its salt in the presence of base to provide a compound of the formula:



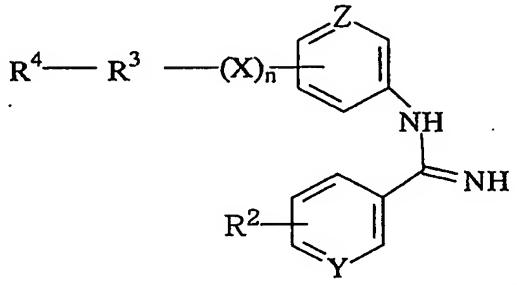
(Ia)

or its salt, in the above formulas,

R^1, R^2, R^3, R^4, W, X, Y, Z, m and n are each as defined above, and

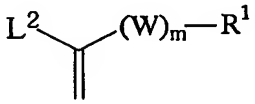
L^1 is a leaving group, or

2) reacting a compound of the formula:



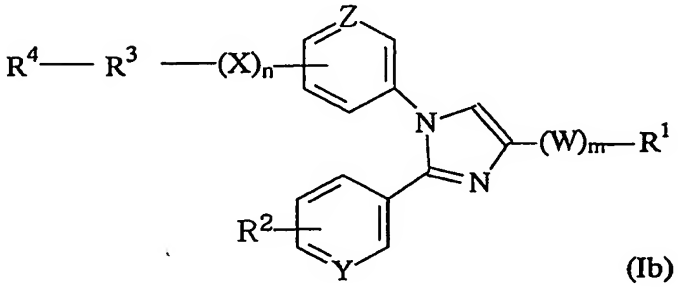
(II)

or its salt with a compound of the formula:



(IV)

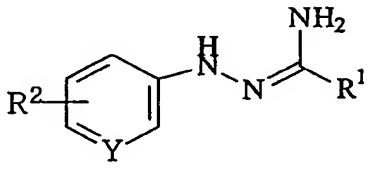
or its salt to provide a compound of the formula:



(Ib)

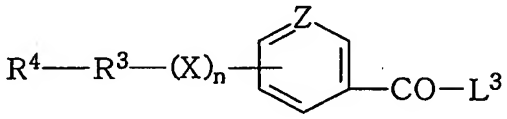
or its salt, in the above formulas,
R^1, R^2, R^3, R^4, W, X, Y, Z, m and n are each as defined above, and
L^2 is a leaving group, or

3) reacting a compound of the formula:



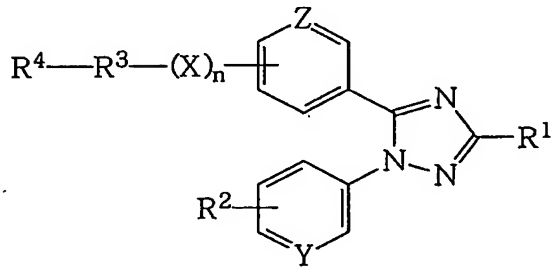
(VI)

its salt with a compound of the formula:



(VII)

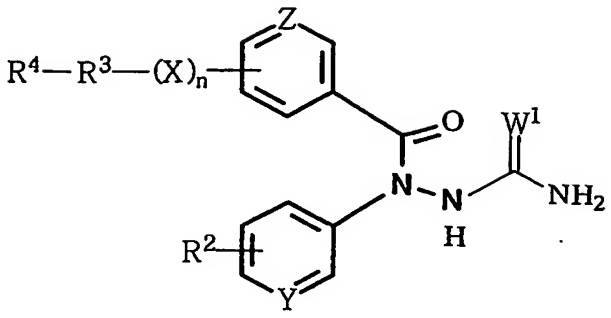
or its salt to provide a compound of the formula:



(Ic)

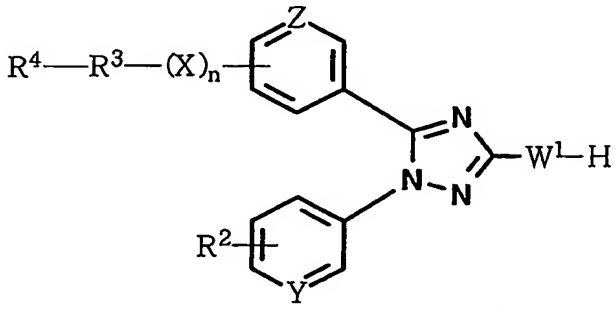
or its salt, in the above formulas,
R^1, R^2, R^3, R^4, W, X, Y, Z, m and n are each as defined above, and
L^3 is a leaving group, or

4) converting a compound of the formula:



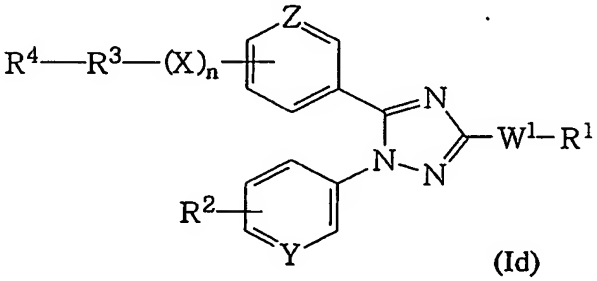
(VIII)

or its salt to a compound of the formula:



(IX)

or its salt, and further condensing the compound (IX) with R^1-L^4 under basic condition to provide a compound of the formula:



(Id)

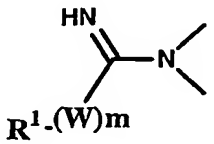
or its salt, in the above formulas,

R^1, R^2, R^3, R^4, X, Y, Z and n are each as defined above,

W^1 is O or S, and

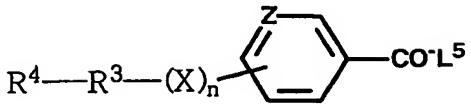
L^4 is a leaving group, or

5) reacting a compound of the formula:



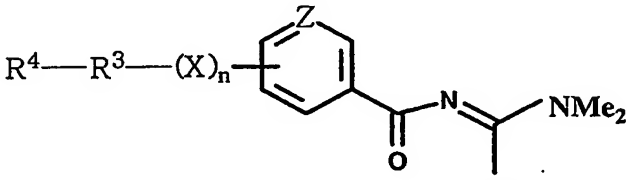
(X)

or its salt with a compound of the formula:



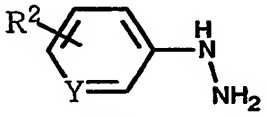
(XI)

or its salt to provide a compound of the formula:



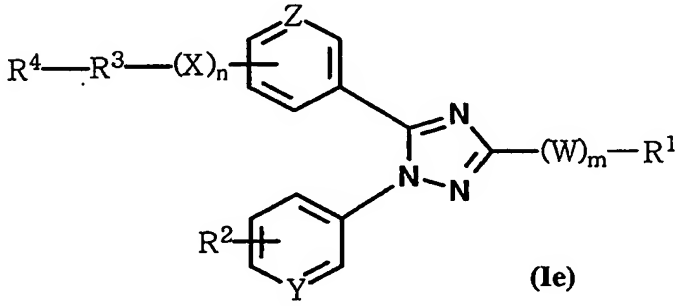
(XII)

or its salt, and further reacting with a compound of the formula:



(XIII)

or its salt to provide a compound of the formula:



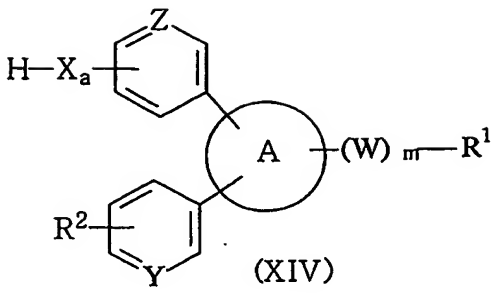
(Ie)

or its salt, in the above formulas,

R^1, R^2, R^3, R^4, W, X, Y, Z, m, n are each as defined above, and

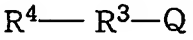
L^5 is a leaving group, or

6) reacting a compound of the formula:



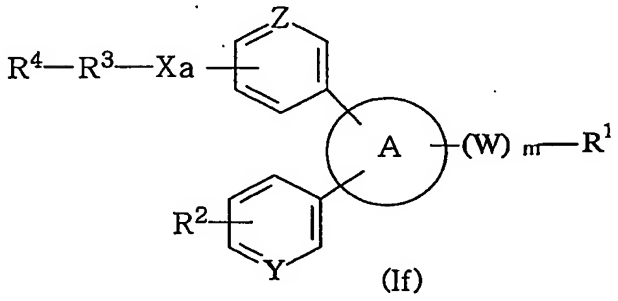
(XIV)

or its salt with a compound of the formula:



(XV)

or its salt to provide a compound of the formula:



(If)

or its salt, in the above formulas,

R^1, R^2, R^3, R^4, W, Y, Z, m, n and

(A) are each as defined above,

Xa is O or S, and

Q is hydroxy or a leaving group.

7. A pharmaceutical composition comprising the compound (I) or its salts of Claim 1, as an active ingredient, in association with a pharmaceutically non-toxic carrier or excipient.

8. A compound of Claim 1 for use as a medicament

9. A method for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases which comprises administering an effective amount of the compound or its salts of Claim 1 to

human beings or animals.

10. Use of the compound of Claim 1 for the manufacture of a medicament for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases in human beings or animals.

11. The analgesic agent comprising the compound of Claim 1, which is usable for treating and/or preventing pains caused by or associated with acute or chronic inflammations without causing gastrointestinal disorders.

12. The analgesic agent of Claim 11, which is usable for treating or preventing pains caused by or associated with rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid spondylitis, gouty arthritis, or juvenile arthritis; lumbago; cervico-omo-brachial syndrome; scapulohumeral periarthritis; pain and tumescence after operation or injury without causing gastrointestinal disorders.

13. A commercial package comprising the pharmaceutical composition containing the compound (I) identified in Claim 1 and a written matter associated therewith, wherein the written matter states that the compound (I) can or should be used for preventing or treating inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 03/15921

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4164 A61K31/4196 C07D233/54 C07D233/90 C07D249/08
C07D403/12 C07D401/04 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03/040110 A (AOKI SATOSHI ;HASHIMOTO NORIO (JP); KUBOTA ARIYOSHI (JP); OMORI HI) 15 May 2003 (2003-05-15) see claim 1 and table on pages 15-16	1-13
X	WO 97/27181 A (SEARLE & CO ;KHANNA ISH K (US); WEIER RICHARD M (US); COLLINS PAUL) 31 July 1997 (1997-07-31) see claim 1, formula (I)	1-13
A	EP 1 099 695 A (THERAMEX) 16 May 2001 (2001-05-16) the whole document	1-13
A	WO 97/38986 A (GRANETO MATTHEW J ;BROWN DAVID L (US); SEARLE & CO (US); TALLEY JO) 23 October 1997 (1997-10-23) see claim 1 and examples 1-12	1-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 April 2004	07/05/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bérillon, L

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 03/15921

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 9 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Continuation of Box I.2

Present claims relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the imidazoles of formula Ia and Ib and to the triazoles of formula Ic, Id or Ie (see claim 6). This restriction covers all the exemplified compounds.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03040110 A	15-05-2003	WO 03040110 A1	15-05-2003
		US 2003191155 A1	09-10-2003
WO 9727181 A	31-07-1997	AT 236130 T	15-04-2003
		AU 730642 B2	08-03-2001
		AU 1573997 A	20-08-1997
		CA 2244837 A1	31-07-1997
		DE 69720428 D1	08-05-2003
		DE 69720428 T2	12-02-2004
		DK 880504 T3	21-07-2003
		EP 1193265 A2	03-04-2002
		EP 0880504 A1	02-12-1998
		ES 2197983 T3	16-01-2004
		JP 2000503987 T	04-04-2000
		NZ 327022 A	29-06-1999
		WO 9727181 A1	31-07-1997
		ZA 9700670 A	16-04-1998
EP 1099695 A	16-05-2001	EP 1099695 A1	16-05-2001
		AT 245148 T	15-08-2003
		AU 1998501 A	06-06-2001
		BR 0015440 A	02-07-2002
		CA 2390649 A1	17-05-2001
		CN 1387517 T	25-12-2002
		CZ 20021591 A3	17-07-2002
		DE 60003949 D1	21-08-2003
		DK 1246809 T3	20-10-2003
		WO 0134577 A1	17-05-2001
		EP 1246809 A1	09-10-2002
		HU 0203376 A2	28-01-2003
		JP 2003513961 T	15-04-2003
		NO 20022202 A	08-05-2002
		NZ 518682 A	25-07-2003
		PT 1246809 T	28-11-2003
		SI 1246809 T1	29-02-2004
		ZA 200203165 A	22-04-2003
WO 9738986 A	23-10-1997	AP 1009 A	21-09-2001
		AT 233743 T	15-03-2003
		AU 734275 B2	07-06-2001
		AU 2722797 A	07-11-1997
		BG 102916 A	31-08-1999
		BR 1100403 A3	25-07-2000
		BR 9708574 A	03-08-1999
		CA 2249009 A1	23-10-1997
		CN 1216043 A ,B	05-05-1999
		CZ 9802710 A3	13-01-1999
		DE 69719496 D1	10-04-2003
		DE 69719496 T2	08-04-2004
		DK 892791 T3	23-06-2003
		EA 3319 B1	24-04-2003
		EE 9800351 A	15-04-1999
		EP 1288206 A1	05-03-2003
		EP 0892791 A1	27-01-1999
		ES 2194195 T3	16-11-2003
		HK 1019741 A1	02-05-2003
		HU 9901807 A2	28-09-1999
		JP 3382624 B2	04-03-2003

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 03/15921

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9738986 A		JP 2000509029 T	18-07-2000
		JP 2003160554 A	03-06-2003
		KR 2000005395 A	25-01-2000
		LT 98142 A ,B	26-07-1999
		LV 12239 A	20-03-1999
		LV 12239 B	20-08-1999
		NO 984727 A	14-12-1998
		NZ 331542 A	29-07-1999
		PL 329276 A1	15-03-1999
		PT 892791 T	30-06-2003
		SI 9720035 A	30-06-1999
		SK 124298 A3	13-04-1999
		TR 9802049 T2	18-01-1999
		US 5932598 A	03-08-1999
		WO 9738986 A1	23-10-1997
		US 6436967 B1	20-08-2002
		ZA 9703146 A	14-04-1998